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(54) Title: A NOVEL MATRIX METALLOPROTEINASE (MMP-25) EXPRESSED IN SKIN CELLS

(57) Abstract: This invention provides nucleic acids and polypeptides encoding a novel family of matrix metalloproteinases herein designated as MMP-25 and variants of the same. MMP-25 is preferentially expressed in skin cells of a mammal, particularly in breast cells and hair follicles. Expression in hair follicles is localized in the Henle layer of cells, indicating a role in hair growth. Also provided are fragments and oligonucleotides useful for identifying and isolating MMP-25-encoding nucleic acids and methods for their use, as well as antibodies that bind specifically to MMP-25 and vectors for expression of MMP-25 polypeptides. Methods of inhibiting MMP-25 activity are provided, including methods useful for inhibiting hair growth.

Other embodiments include a nucleic acid fragment or oligonucleotide comprising at least 15 contiguous nucleotides selected from positions 1-653 of SEQ ID NO:3 or a compliment thereof; and a nucleic acid fragment or oligonucleotide comprising at least 15 contiguous nucleotides selected from positions 1-741 or 1573-1841 of SEQ ID NO:5 or a compliment thereof. Particular embodiments of these nucleic acid fragments or oligonucleotides include any of the above where the length is at least 18, 24, 30, 50 or greater than 50 nucleotides.

In a related aspect, the invention provides a nucleic acid fragment or oligonucleotide encoding a peptide comprised of at least 8 contiguous amino acids of the sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, with the proviso that said nucleic acid fragment is not SEQ ID NO:15 or 16. Particular embodiments of this aspect include nucleic acid fragments or oligonucleotides encoding a peptides comprised of at least 10, 15, or 20 amino acids. Still more particular embodiments include the aforementioned nucleic acid fragments wherein the encoded peptide comprises contiguous amino acids from positions 1-61, 98-111, 161-170 or 261-513 of SEQ ID NO:6.

In a similarly related aspect, the invention provides a nucleic acid fragment or oligonucleotide encoding a peptide comprised of at least 8 contiguous amino acids from positions 1-200 of SEQ ID NO:4. Particular embodiments of this aspect also include fragments or oligonucleotides comprised of at least 10, 15 or 20 amino acids. Also included within this aspect are any one of these fragments or oligonucleotides wherein the peptide comprises contiguous amino acids from positions 1-61 or 98-111 of SEQ ID NO:4. In a further related aspect, the invention provides a nucleic acid fragment or oligonucleotide encoding a peptide comprised of at least 8 contiguous amino acids from positions 1-243 of SEQ ID NO:6. Particular embodiments of this aspect also include fragments or oligonucleotides comprised of at least 10, 15 or 20 amino acids. Also included within this aspect are any one of these fragments or oligonucleotides wherein the peptide comprises contiguous amino acids positions 1-61 or 98-111, or 161-170 of SEQ ID NO:6.

The invention also includes methods of use of the aforementioned nucleic acids. In one aspect, the invention provides a method of identifying a nucleic acid encoding all or a part of a metalloproteinase, comprising the steps of:(1) hybridizing a nucleic acid sample to the nucleic acids mentioned above and (2) identifying a sequence that hybridizes thereto. In a typical practice of this method, the step of identifying includes performing a polymerase chain reaction to amplify a sequence containing the sequence that hybridizes. Thus, the invention also includes a pair of primers that specifically amplifies all or a portion of a MMP-25 nucleic acid molecule.

In another aspect, the invention provides vectors containing MMP-25 and related sequences. More specifically, the invention provides a recombinant nucleic acid vector containing the aforementioned MMP-25 nucleic acid sequences. In a typical embodiment, the recombinant nucleic acid vector is an expression vector containing a promoter operably linked to the MMP-25 nucleic acid sequences. In another typical embodiment, the vector is selected from the group consisting of:plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors. In a related aspect, the invention provides for a host cell containing any of the aforementioned vectors.

The vectors provided by the present invention are useful for producing MMP-25 polypeptides. Another aspect of the invention therefore includes a method of producing a MMP-25 polypeptide comprising the step of culturing a host cell comprising one of the aforementioned vectors, comprising a promoter operably linked to the MMP-25 sequence, under conditions and for a time sufficient to produce the MMP-25 polypeptide. In a preferred practice, the method further includes the step of purifying the MMP-25 polypeptide.

Accordingly, the invention also provides for a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6; (b) an amino acid sequence having at least 50% identity to the polypeptide of (a) or (b); (c) a sequence encoding a functional fragment of the polypeptide of (a) or (b); and (d) an amino acid

sequence encoded by a nucleic acid that hybridizes under conditions of normal stringency to the foregoing. More typical embodiments of these polypeptides include those having at least 50%, 60%, 70%, 80%, 90%, or 95% identity to the polypeptide according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6. In particular embodiments, identity is calculated according a MEGALIGN algorithm using a gap penalty and gap length penalty each set at a value of 10.

The polypeptides of the present invention are useful for raising antibodies thereto which are specific for MMP-25 proteins. Accordingly, another aspect of the invention is an antibody that binds to a MMP, wherein said antibody specifically binds to one of the aforementioned polypeptides. In one embodiment, the antibody is a monoclonal antibody. Typically the antibody will bind to a type 25 MMP with a higher affinity than it binds to a non type 25 MMP. The antibody is also typically, a murine or human antibody. Related aspects include an antibody selected from the group consisting of $F(ab')_2$, $F(ab)_2$, Fab' Fab and Fv, and a hybridoma which produces the aforementioned monoclonal antibody.

Antibodies to MMP-25 polypeptides are useful in another aspect of the invention, which is a method of identifying a type 25 MMP polypeptide comprising incubating an antibody that binds to MMP-25 polypeptide with a sample containing protein for a time sufficient to permit said antibody to bind the type 25 MMP present in the sample. In a typical practice of this method, the antibody is bound to a solid support and optionally may be labeled.

In another aspect, the invention provides for fusion proteins containing a portion of a MMP-25 polypeptide which is useful for example, in raising antibodies to particular segments of a MMP-25 polypeptide. Accordingly the invention also includes a fusion protein, comprising a first MMP-25 polypeptide segment comprised of at least eight contiguous amino acids of a MMP-25 polypeptide, fused in-frame to a second polypeptide segment comprised of a non MMP-25 polypeptide. The size of the first polypeptide segment of the fusion protein is typically at least 10, 15, or 20 amino acids in length.

In a different aspect, the nucleic acid sequences of the present invention provide for derivative nucleic acids useful for modulating or inhibiting the expression of an MMP-25 polypeptide in a cell. More specifically, the invention provides for a ribozyme that cleaves RNA encoding the aforementioned MMP-25 polypeptides. This aspect also includes a nucleic acid molecule comprising a sequence that encodes such a ribozyme and a vector comprising said nucleic acid molecule. In a related aspect, the invention provides an antisense nucleic acid molecule comprising a sequence that is antisense to a portion of the MMP-25 nucleic acids described above, a vector comprising the antisense molecule, and vectors wherein the aforementioned ribozyme or antisense nucleic acid is operably linked to a promoter. Typical embodiments of these vectors are selected from the group consisting of plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors. The invention also provides for a host cell comprising such a vector.

In yet another aspect, the invention provides a nucleic acid molecule comprising a sequence that encodes at a peptide of at least 27 amino acids in length, wherein said peptide is a consensus sequence for a Zn-binding domain of a MMP. Particular embodiments of this aspect includes SEQ ID NO:7 or SEQ ID NO:8 which are also useful for obtaining additional MMP sequences. Accordingly, the invention further provides a method of identifying a nucleic acid encoding all or a part of a MMP comprising, identifying a sequence encoded by the aforementioned consensus sequence, and cloning a sequence containing the identified sequence from a cDNA library.

In still another aspect, the MMP-25 sequences of the present invention provide for a method of inhibiting a catalytic activity of a MMP polypeptide in a cell comprising, administering an agent to the cell that inhibits a catalytic activity of the MMP, with the proviso that said agent inhibits the catalytic activity of a MMP-25 polypeptide to a greater extent than it inhibits the activity of at least one non-type 25 MMP. In a typical practice of this method, the MMP-25 polypeptide is preferentially expressed in the cell relative to the non-type 25 MMP. In one embodiment, the agent is

DETAILED DESCRIPTION OF THE INVENTION

The following provides definitions of certain terms, and lists certain abbreviations used herein.

"Molecule" should be understood to include proteins or peptides (*e.g.*, antibodies, recombinant binding partners, peptides with a desired binding affinity) nucleic acids (*e.g.*, DNA, RNA, chimeric nucleic acid molecules, and nucleic acid analogues such as PNA); and organic or inorganic compounds.

"MMP-25" or "Type 25 MMP" should be understood to include any polypeptide, or nucleic acid encoding a polypeptide of the MMP family, having at least 50%, 60%, 70%, 80%, 90%, or 95% amino acid identity to any one the polypeptides provided herein as SEQ ID NO:2, 4, or 6. These polypeptides will also have less than 50% sequence identity to known MMP members designated as MMP 1-3, or 7 -22. Example sequence comparisons and identity calculations are shown in Table 1 and Figure 3.

"Non-type 25 MMP" refers to a polypeptide having less sequence identity to any of the MMPs according to SEQ ID NO:2, 4 or 6 than to another type of MMP, for example, MMPs 1-3 or 7-22. A non-type 25 MMP typically has less than 50% identity to any of the SEQ ID NO:2, 4 or 6.

"Vector" refers to an assembly that is capable of delivering a recombinant nucleic acid molecule to a cell wherein the nucleic acid molecule is maintained, either as part of an independently replicating element or as integrated into the genome of the cell. An "expression vector" is a vector that further includes transcriptional promoter elements operably linked to a recombinant nucleic acid of interest. The vector may be composed of either deoxyribonucleic acids ("DNA"), ribonucleic acids ("RNA"), or a combination of the two (*e.g.*, a DNA-RNA chimeric). Optionally, the vector may include a polyadenylation sequence, one or more restriction sites, as well as one or more selectable markers such as neomycin phosphotransferase or hygromycin phosphotransferase. Additionally, depending on the host cell chosen and the vector employed, other genetic elements such as an origin of replication, additional nucleic acid restriction sites, enhancers, sequences conferring inducibility of

transcription, and selectable markers, may also be incorporated into the vectors described herein.

An "isolated nucleic acid molecule" is a nucleic acid molecule that is not integrated in the genomic DNA of an organism. For example, a DNA molecule that encodes a MMP-25 polypeptide that has been separated from the genomic DNA of a eukaryotic cell is an isolated DNA molecule. Another example of an isolated nucleic acid molecule is a chemically-synthesized nucleic acid molecule that is not integrated in the genome of an organism. The isolated nucleic acid molecule may be genomic DNA, cDNA, RNA, or composed at least in part of nucleic acid analogs.

An "isolated polypeptide" is a polypeptide that has been removed by at least one step from its original environment. For example, a naturally occurring protein is isolated if it is separated from some or all of the coexisting material in the natural system such as carbohydrate, lipid, or other proteinaceous impurities associated with the polypeptide in nature. Within certain embodiments, a particular protein preparation contains an isolated polypeptide if it appears nominally as a single band on SDS-PAGE gel with Coomassie Blue staining.

A "functional fragment" of a MMP-25 polypeptide refers to a portion of a MMP-25 polypeptide that either (1) possesses a catalytic activity of a MMP-25 polypeptide, or (2) specifically binds with an anti-MMP-25 antibody.

"Humanized antibodies" are recombinant proteins in which murine complementarity determining regions of monoclonal antibodies have been transferred from heavy and light variable chains of the murine immunoglobulin into a human variable domain.

As used herein, an "antibody fragment" is a portion of an antibody such as $F(ab')_2$, $F(ab)_2$, Fab', Fab, and the like. Regardless of structure, an antibody fragment binds with the same antigen that is recognized by the intact antibody. For example, an anti-MMP-25 monoclonal antibody fragment binds with an epitope of MMP-25 .

The term "antibody fragment" also includes any synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a

corresponds to the Zn/Ca-binding domain. The conserved regions of both Zn-binding domains varied from the consensus sequences first used for the search. Therefore, use of Zn-binding domain consensus sequences are useful for identifying divergent MMPs so long as the MMP sequence contains at least one sequence having at least about 50% identity with the consensus sequences.

Despite conservation in the aforementioned polypeptide domain regions, the remainder of the MMP-25 sequences show low similarity to other MMP family members. Sequence identity was calculated as a percentage using the MEGALIGN algorithm provided with sequence alignment program DNASTAR (Madison, WI) using a Clustal method with the gap penalty and gap length penalty each set at 10. Gaps were established to maximize the number of sequence matches between the MMP-25(l) source (SEQ ID NO:5) and other MMP query sequences (SEQ ID NOs 19-36). The results are shown in Table 1.

Table 1

Percent Amino Acid Sequence Identity of MMP-25(l) to Other MMP Sequences

MMP	Names indicated in Figure 3	Percent Identity to MMP-25(l)
MMP-25(s)*	Contig 355 short form	99.2
MMP-1	COLL1.HUM.PRO	45.0
MMP-8	COLL2.HUM.PRO	44.5
MMP-13	COLL3.HUM.PRO	43.5
MMP-7	MATRHUM.PRO	39.7
MMP-12	METAHUM.PRO	43.2
MMP-3	STO1HUM.PRO	46.8
MMP-10	STO2HUM.PRO	46.6
MMP-11	STO3HUM.PRO	24.2
MMP-14	MTM1HUM.PRO	26.3
MMP-15	MTM2HUM.PRO	27.1
MMP-16	MTM3HUM.PRO	26.1

MMP-17P	17P	22.0
MMP-18P	18P	22.6
MMP-20P	20P	43.5
MMP-21P	21P	18.6
MMP-22P	22P	16.9
MMP-2	GELAHUM.PRO	31.6
MMP-9	GELBHUM.PRO	23.2

*MMP-25(s) is provided herein

The highest overall sequence identity to any other known MMP is 46% to members of the stomelysin subfamily of MMPs which include MMP3, MMP10 and MMP11. A comparison of MMP-25(l) to other sequences using a different sequence comparison algorithm, namely Blastn or Blastp, also shows MMP-25 sequences to have low sequence identity with respect to other known MMP. More specifically, the greatest sequence identity obtained was 58% to a *Gallus gallus* MMP sequence. These programs were run using default settings. However these programs do not return an identity score that evaluates the whole of the MMP-25 sequence, but only evaluates those portions of MMP-25 sequences where some level of identity to the comparison sequence can be found. Typically, there is no significant identity to other MMP sequences in the region corresponding to positions 481-510 of SEQ ID NO:6 (which corresponds to positions 438-470 of SEQ ID NO:4). Accordingly, the overall sequence identity of MMP-25 to other known sequences is less than 50% when the whole of the MMP-25 sequence is compared to a other MMP sequences using BLAST programs as well as MEGALIGN.

Figure 3 illustrates patterns of sequence identity between the MMP-25 sequences of the present invention in comparison to eighteen other known MMP sequences. The comparison indicates regions where sequence identity is high, which include the aforementioned domains common amongst MMP proteins which are also depicted Figure 3. In addition, Figure 3 indicates that there are regions of low identity between MMP-25 and other MMP sequences. Regions of low identity are particularly useful for identifying MMP-25 family members by hybridization or antibody

MMP-25 antibody. For example, the MMP-25 polypeptide encoded by the 833 nucleotide fragment (SEQ ID NO:2) is a functional fragment of the larger MMP-25 disclosed above as SEQ ID NO 6.

Fragments and oligonucleotides

Also provided herein are nucleic acid fragments or oligonucleotides useful as probes and primers for identifying or obtaining MMP-25 sequences. More specifically, a nucleic acid fragment or oligonucleotide should comprise at least 15 contiguous nucleotides of SEQ ID NO:1 or SEQ ID NO:3, or SEQ ID NO:5 with the proviso that said nucleic acid fragment is not SEQ ID NO:15 or 16. More particular embodiments include fragments or oligonucleotides such as positions 1-653 of SEQ ID NO:3 or 1-741 or 1573-1841 of SEQ ID NO:5. Particular embodiments of these nucleic acid fragments or oligonucleotides include any of the above where the length is at least 18, 24, 30, 50 or greater than 50 nucleotides. Complements of the above sequences are also included.

Another embodiment of nucleic acid fragments or oligonucleotides of this invention include those that encode a peptide epitope that can be detected, for example, by the ability to specifically bind to a MMP-25 antibody or which can be used to elicit an immune response in an animal. Useful peptide epitopes are those capable of eliciting antibodies that specifically bind to the peptide or polypeptide comprised of the same, or that are capable of eliciting a T-cell response. Peptide sequences of 8 or more amino acids are useful in this regard since it is generally understood by those skilled in the art that 8 amino acids is the lower size limit for a peptide to interact with the major histocompatibility complex (MHC). More preferred embodiments include nucleic acid fragments or oligonucleotides encoding at least 10, 15 or 20 amino acids.

Therefore, the present invention provides for nucleic acid fragments or oligonucleotides encoding a peptide comprised of at least 8 contiguous amino acids of the sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, with the proviso that said nucleic acid fragment is not SEQ ID NO:15 or 16. Particular embodiments of this aspect include nucleic acid fragments or oligonucleotides encoding

a peptide comprised of at least 10, 15, or 20 amino acids. Still more particular embodiments include nucleic acid fragments wherein the encoded peptide comprises sequences particularly distinctive of MMP-25 polypeptides. These include sequence such as those encoding peptides from positions 1-243 of SEQ ID NO:6. Other preferred sequences that are distinctive of MMP-25 include those encoding peptides from positions 1-61, 98-111, 161-170 or 261-513 of SEQ ID NO:6. Also included in this regard are nucleic acids encoding at least 8, 10, 15 or 20 amino acids from positions 1-200 of SEQ ID NO:4, with preferred fragments or oligonucleotides encoding a peptide from positions 1-61 or 98-111 of SEQ ID NO:4.

Methods of use of nucleic acids, fragments and oligonucleotides

The aforementioned nucleic acids fragments and oligonucleotides are useful for the identification or isolation of MMP-25 nucleic acids, polypeptides and variants thereof. Typically, the nucleic acid fragments are used for probes for hybridization to sample sequences or as primers for PCR reactions. Thus, the invention provides for methods of identifying a nucleic acid encoding all or a part of a metalloproteinase, comprising the steps of:(1) hybridizing a nucleic acid sample to the nucleic acids mentioned above and (2) identifying a sequence that hybridizes thereto. In a typical practice of this method, the step of identifying includes performing a polymerase chain reaction to amplify a sequence containing the sequence that hybridizes. Thus the invention also includes at least one pair of primers that specifically amplifies all or a portion of a MMP-25 nucleic acid molecule.

In addition, as discussed above, the present invention includes consensus sequences for a Zn or Zn/Ca-binding domain of MMPs. The consensus sequences used are unique, and permit identification and isolation of MMP sequences having at least 50% identity to the consensus sequences. Therefore, another aspect of the present invention provides a nucleic acid comprising a sequence that encodes a peptide of at least 27 amino acids in length, wherein said peptide is a consensus sequence for a Zn-binding domain of a MMP. Particular embodiments of this aspect include SEQ ID NO:7 or SEQ ID NO:8. In a related aspect, the invention provides a general method of

identifying a nucleic acid encoding all or a part of a MMP that includes the steps of identifying a sequence encoded by the aforementioned consensus sequences, and cloning a sequence containing the identified sequence from a cDNA library.

Identification and Isolation of MMP-25 nucleic acids

DNA molecules encoding a gene can be obtained by screening a human cDNA or genomic library using polynucleotide probes based upon the aforementioned MMP-25 sequences, fragments and oligonucleotides.

For example, the first step in the preparation of a cDNA library is to isolate RNA using methods well-known to those of skill in the art. In general, RNA isolation techniques provide a method for breaking cells, a means of inhibiting RNase-directed degradation of RNA, and a method of separating RNA from DNA, protein, and polysaccharide contaminants. For example, total RNA can be isolated by freezing tissue in liquid nitrogen, grinding the frozen tissue with a mortar and pestle to lyse the cells, extracting the ground tissue with a solution of phenol/chloroform to remove proteins, and separating RNA from the remaining impurities by selective precipitation with lithium chloride (see, for example, Ausubel et al. (eds.), *Short Protocols in Molecular Biology, 3rd Edition*, pages 4-1 to 4-6 (John Wiley & Sons 1995) ["Ausubel (1995)"]; Wu et al., *Methods in Gene Biotechnology*, pages 33-41 (CRC Press, Inc. 1997) ["Wu (1997)"]).

Alternatively, total RNA can be isolated by extracting ground tissue with guanidinium isothiocyanate, extracting with organic solvents, and separating RNA from contaminants using differential centrifugation (see, for example, Ausubel (1995) at pages 4-1 to 4-6; Wu (1997) at pages 33-41).

In order to construct a cDNA library, poly(A)$^+$ RNA is isolated from a total RNA preparation. Poly(A)$^+$ RNA can be isolated from total RNA by using the standard technique of oligo(dT)-cellulose chromatography (see, for example, Ausubel (1995) at pages 4-11 to 4-12).

Double-stranded cDNA molecules are synthesized from poly(A)$^+$ RNA using techniques well known to those in the art. (see, for example, Wu (1997) at pages 41-46). Commercially available kits can be used to synthesize double-stranded cDNA

molecules. For example, such kits are available from Life Technologies, Inc. (Gaithersburg, Maryland), Clontech Laboratories, Inc. (Palo Alto, California), Promega Corporation (Madison, Wisconsin) and Stratagene Cloning Systems (La Jolla, California).

The basic approach for obtaining MMP-25 cDNA clones can be modified by constructing a subtracted cDNA library which is enriched in MMP cDNA molecules. Techniques for constructing subtracted libraries are well-known to those of skill in the art (see, for example, Sargent, "Isolation of Differentially Expressed Genes," in *Meth. Enzymol. 152*:423, 1987, and Wu et al. (eds.), "Construction and Screening of Subtracted and Complete Expression cDNA Libraries," in *Methods in Gene Biotechnology*, pages 29-65 (CRC Press, Inc. 1997)).

Various cloning vectors are appropriate for the construction of a cDNA library. For example, a cDNA library can be prepared in a vector derived from bacteriophage, such as a λgt10 vector (see, for example, Huynh et al., "Constructing and Screening cDNA Libraries in λgt10 and λgt11," in *DNA Cloning:A Practical Approach Vol. I*, Glover (ed.), page 49 (IRL Press, 1985); Wu (1997) at pages 47-52).

Alternatively, double-stranded cDNA molecules can be inserted into a plasmid vector, such as a pBluescript vector (Stratagene Cloning Systems; La Jolla, California), a LambdaGEM-4 (Promega Corp.; Madison, Wisconsin) or other commercially available vectors. Suitable cloning vectors also can be obtained from the American Type Culture Collection (Rockville, Maryland).

In order to amplify the cloned cDNA molecules, the cDNA library is inserted into a prokaryotic host, using standard techniques. For example, a cDNA library can be introduced into competent *E. coli* DH5 cells, which can be obtained from Life Technologies, Inc. (Gaithersburg, Maryland).

A human genomic DNA library can be prepared by means well-known in the art (see, for example, Ausubel (1995) at pages 5-1 to 5-6; Wu (1997) at pages 307-327). Genomic DNA can be isolated by lysing tissue with the detergent Sarkosyl, digesting the lysate with proteinase K, clearing insoluble debris from the lysate by

centrifugation, precipitating nucleic acid from the lysate using isopropanol, and purifying resuspended DNA on a cesium chloride density gradient.

DNA fragments that are suitable for the production of a genomic library can be obtained by the random shearing of genomic DNA or by the partial digestion of genomic DNA with restriction endonucleases. Genomic DNA fragments can be inserted into a vector, such as a bacteriophage or cosmid vector, in accordance with conventional techniques, such as the use of restriction enzyme digestion to provide appropriate termini, the use of alkaline phosphatase treatment to avoid undesirable joining of DNA molecules, and ligation with appropriate ligases. Techniques for such manipulation are well-known in the art (see, for example, Ausubel (1995) at pages 5-1 to 5-6; Wu (1997) at pages 307-327).

Nucleic acid molecules that encode a MMP-25 gene can also be obtained using the polymerase chain reaction (PCR) with oligonucleotide primers having nucleotide sequences that are based upon the nucleotide sequences of the human MMP-25 gene, as described herein. General methods for screening libraries with PCR are provided by, for example, Yu et al., "Use of the Polymerase Chain Reaction to Screen Phage Libraries," in *Methods in Molecular Biology, Vol. 15:PCR Protocols:Current Methods and Applications*, White (ed.), pages 211-215 (Humana Press, Inc. 1993). Techniques for using PCR to isolate related genes are described by, for example, Preston, "Use of Degenerate Oligonucleotide Primers and the Polymerase Chain Reaction to Clone Gene Family Members," in *Methods in Molecular Biology, Vol. 15:PCR Protocols:Current Methods and Applications*, White (ed.), pages 317-337 (Humana Press, Inc. 1993). Examples 1 and 2 illustrate one approach to obtaining MMP-25 nucleic acids using RT-PCR.

Alternatively, human genomic libraries can be obtained from commercial sources such as Research Genetics (Huntsville, AL) and the American Type Culture Collection (Rockville, Maryland).

A library containing cDNA or genomic clones can be screened with one or more polynucleotide probes based upon SEQ ID NO:1, 3, or 5 using standard methods (see, for example, Ausubel (1995) at pages 6-1 to 6-11).

Anti-MMP-25 antibodies, produced as described below, can also be used to isolate DNA sequences that encode MMP-25 genes from cDNA libraries. For example, the antibodies can be used to screen λgt11 expression libraries, or the antibodies can be used for immunoscreening following hybrid selection and translation (see, for example, Ausubel (1995) at pages 6-12 to 6-16; Margolis et al., "Screening λ expression libraries with antibody and protein probes," in *DNA Cloning 2:Expression Systems, 2nd Edition*, Glover et al. (eds.), pages 1-14 (Oxford University Press 1995)).

The sequence of a MMP-25 cDNA or MMP-25 genomic fragment can be determined using standard methods. The identification of genomic fragments containing a MMP-25 promoter or regulatory element can be achieved using well-established techniques, such as deletion analysis (Ausubel (1995)).

A MMP-25 gene can also be obtained by synthesizing DNA molecules using mutually priming long oligonucleotides and the nucleotide sequences described herein (Ausubel (1995) at pages 8-8 to 8-9). Established techniques using the polymerase chain reaction provide the ability to synthesize DNA molecules at least two kilobases in length (Adang et al., *Plant Molec. Biol. 21*:1131, 1993; Bambot et al., *PCR Methods and Applications 2*:266, 1993; Dillon et al., "Use of the Polymerase Chain Reaction for the Rapid Construction of Synthetic Genes," in *Methods in Molecular Biology, Vol. 15:PCR Protocols:Current Methods and Applications*, White (ed.), pages 263-268 (Humana Press, Inc. 1993); Holowachuk et al., *PCR Methods Appl. 4*:299, 1995).

Production of Variants

Nucleic acid molecules encoding variant MMP-25 nucleic acids can be produced by screening various cDNA or genomic libraries with polynucleotide probes having nucleotide sequences based upon SEQ ID NO:1, 3 or 5 and the fragments or oligonucleotides derived therefrom described above. MMP-25 nucleic acids and variants can also be constructed synthetically. For example, a nucleic acid molecule can be obtained that encodes a polypeptide having a conservative amino acid change, compared with the amino acid sequence of SEQ ID NO:2, 4, or 6. That is, variants can

performed in 0.5xSSC (1xSSC = 150 mM sodium chloride, 15 mM trisodium citrate) or in 0.5xSSPE at 55-60°C. Stringent hybridization conditions typically hybridize 1-2x SSPE (or equivalent salt concentration) overnight at 48-65°C, with or without a strand denaturant such 50% formamide, followed by a wash in 0.1-0.2% SSC at about 65°C.

Vectors

The invention provides for recombinant nucleic acid vectors comprising the aforementioned MMP-25 nucleic acids and related sequences. In a typical embodiment, the vector is an expression vector containing a promoter operably linked to the MMP-25 nucleic acid sequence for use in expressing a MMP-25 RNA, polypeptide or fragment thereof. The vector may be selected from any type of vector depending on intended use and host cell type. These include plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors.

To express a MMP-25 gene, a nucleic acid molecule encoding the polypeptide must be operably linked to regulatory sequences that control transcriptional expression in an expression vector and then introduced into a host cell. In addition to transcriptional regulatory sequences, such as promoters and enhancers, expression vectors can include translational regulatory sequences and a marker gene which is suitable for selection of cells that carry the expression vector.

Expression vectors that are suitable for production of a foreign protein in eukaryotic cells typically contain (1) prokaryotic DNA elements coding for a bacterial replication origin and an antibiotic resistance marker to provide for the growth and selection of the expression vector in a bacterial host; (2) eukaryotic DNA elements that control initiation of transcription, such as a promoter; and (3) DNA elements that control the processing of transcripts, such as a transcription termination/polyadenylation sequence.

MMP-25 nucleic acids of the present invention are preferably expressed in mammalian cells. Examples of mammalian host cells include African green monkey kidney cells (Vero; ATCC CRL 1587), human embryonic kidney cells (293-HEK; ATCC CRL 1573), baby hamster kidney cells (BHK-21; ATCC CRL 8544), canine kidney cells

(MDCK; ATCC CCL 34), Chinese hamster ovary cells (CHO-K1; ATCC CCL61), rat pituitary cells (GH1; ATCC CCL82), HeLa S3 cells (ATCC CCL2.2), rat hepatoma cells (H-4-II-E; ATCC CRL 1548) SV40-transformed monkey kidney cells (COS-1; ATCC CRL 1650) and murine embryonic cells (NIH-3T3; ATCC CRL 1658).

For a mammalian host, the transcriptional and translational regulatory signals may be derived from viral sources, such as adenovirus, bovine papilloma virus, simian virus, or the like, in which the regulatory signals are associated with a particular gene which has a high level of expression. Suitable transcriptional and translational regulatory sequences also can be obtained from mammalian genes, such as actin, collagen, myosin, and metallothionein genes.

Transcriptional regulatory sequences include a promoter region sufficient to direct the initiation of RNA synthesis. Suitable eukaryotic promoters include, for example, the promoter of the mouse metallothionein I gene (Hamer et al., *J. Molec. Appl. Genet. 1*:273, 1982), the *TK* promoter of *Herpes* virus (McKnight, *Cell 31*:355, 1982), the *SV40* early promoter (Benoist et al., *Nature 290*:304, 1981), the *Rous* sarcoma virus promoter (Gorman et al., *Proc. Nat'l Acad. Sci. USA 79*:6777, 1982), the cytomegalovirus promoter (Foecking et al., *Gene 45*:101, 1980), and the mouse mammary tumor virus promoter (see, generally, Etcheverry, "Expression of Engineered Proteins in Mammalian Cell Culture," in *Protein Engineering:Principles and Practice*, Cleland et al. (eds.), pages 163-181 (John Wiley & Sons, Inc. 1996)).

Alternatively, a prokaryotic promoter, such as the bacteriophage T3 RNA polymerase promoter, can be used to control MMP-25 gene expression in mammalian cells if the prokaryotic promoter is regulated by a eukaryotic promoter (Zhou et al., *Mol. Cell. Biol. 10*:4529, 1990; Kaufman et al., *Nucl. Acids Res. 19*:4485, 1991).

MMP-25 genes may also be expressed in bacterial, yeast, insect, or plant cells. Suitable promoters that can be used to express MMP-25 polypeptides in a prokaryotic host are well-known to those of skill in the art and include promoters capable of recognizing the T4, T3, Sp6 and T7 polymerases, the P_R and P_L promoters of bacteriophage lambda, the *trp*, *recA*, heat shock, *lacUV5*, *tac*, *lpp-lacSpr*, *phoA*, and *lacZ* promoters of *E. coli*, promoters of *B. subtilis*, the promoters of the bacteriophages

of *Bacillus*, *Streptomyces* promoters, the *int* promoter of bacteriophage lambda, the *bla* promoter of pBR322, and the CAT promoter of the chloramphenicol acetyl transferase gene. See Glick, *J. Ind. Microbiol. 1*:277, 1987, Watson et al., *Molecular Biology of the Gene, 4th Ed.* (Benjamin Cummins 1987), and by Ausubel et al. (1995).

Preferred prokaryotic hosts include *E. coli* and *B. subtilus*. Suitable strains of *E. coli* include BL21(DE3), BL21(DE3)pLysS, BL21(DE3)pLysE, DH1, DH4I, DH5, DH5I, DH5IF', DH5IMCR, DH10B, DH10B/p3, DH11S, C600, HB101, JM101, JM105, JM109, JM110, K38, RR1, Y1088, Y1089, CSH18, ER1451, and ER1647 (see, for example, Brown (Ed.), *Molecular Biology Labfax* (Academic Press 1991)). Suitable strains of *Bacillus subtilus* include BR151, YB886, MI119, MI120, and B170 (see, for example, Hardy, "Bacillus Cloning Methods," in *DNA Cloning:A Practical Approach*, Glover (Ed.) (IRL Press 1985)).

Methods for expressing proteins in prokaryotic hosts are well-known to those of skill in the art (see, for example, Williams et al., "Expression of foreign proteins in *E. coli* using plasmid vectors and purification of specific polyclonal antibodies," in *DNA Cloning 2:Expression Systems, 2nd Edition*, Glover et al. (eds.), page 15 (Oxford University Press 1995); Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies:Principles and Applications*, page 137 (Wiley-Liss, Inc. 1995); and Georgiou, "Expression of Proteins in Bacteria," in *Protein Engineering:Principles and Practice*, Cleland et al. (eds.), page 101 (John Wiley & Sons, Inc. 1996)).

The baculovirus system provides an efficient means to introduce cloned MMP-25 genes into insect cells. Suitable expression vectors are based upon the *Autographa californica* multiple nuclear polyhedrosis virus (AcMNPV), and contain well-known promoters such as *Drosophila* heat shock protein (hsp) 70 promoter, *Autographa californica* nuclear polyhedrosis virus immediate-early gene promoter (*ie-1*) and the delayed early *39K* promoter, baculovirus p10 promoter, and the *Drosophila* metallothionein promoter. Suitable insect host cells include cell lines derived from IPLB-*Sf*-21, a *Spodoptera frugiperda* pupal ovarian cell line, such as *Sf9* (ATCC CRL 1711), *Sf*21AE, and *Sf*21 (Invitrogen Corporation; San Diego, CA), as well as

Drosophila Schneider-2 cells. Established techniques for producing recombinant proteins in baculovirus systems are provided by Bailey et al., "Manipulation of Baculovirus Vectors," in *Methods in Molecular Biology, Volume 7:Gene Transfer and Expression Protocols*, Murray (ed.), pages 147-168 (The Humana Press, Inc. 1991), by Patel et al., "The baculovirus expression system," in *DNA Cloning 2:Expression Systems, 2nd Edition*, Glover *et al.* (eds.), pages 205-244 (Oxford University Press 1995), by Ausubel (1995) at pages 16-37 to 16-57, by Richardson (ed.), *Baculovirus Expression Protocols* (The Humana Press, Inc. 1995), and by Lucknow, "Insect Cell Expression Technology," in *Protein Engineering:Principles and Practice*, Cleland et al. (eds.), pages 183-218 (John Wiley & Sons, Inc. 1996).

Promoters for expression in yeast include promoters from *GAL1* (galactose), *PGK* (phosphoglycerate kinase), *ADH* (alcohol dehydrogenase), *AOX1* (alcohol oxidase), HIS4 (histidinol dehydrogenase), and the like. Many yeast cloning vectors have been designed and are readily available. These vectors include YIp-based vectors, such as YIp5, YRp vectors, such as YRp17, YEp vectors such as YEp13 and YCp vectors, such as YCp19. One skilled in the art will appreciate that there are a wide variety of suitable vectors for expression in yeast cells.

Expression vectors can also be introduced into plant protoplasts, intact plant tissues, or isolated plant cells. General methods of culturing plant tissues are provided, for example, by Miki et al., "Procedures for Introducing Foreign DNA into Plants," in *Methods in Plant Molecular Biology and Biotechnology*, Glick et al. (eds.), pages 67-88 (CRC Press, 1993).

An expression vector can be introduced into host cells using a variety of standard techniques including calcium phosphate transfection, liposome-mediated transfection, microprojectile-mediated delivery, electroporation, and the like. Preferably, the transfected cells are selected and propagated to provide recombinant host cells that comprise the expression vector stably integrated in the host cell genome. Techniques for introducing vectors into eukaryotic cells and techniques for selecting such stable transformants using a dominant selectable marker are described, for example, by Ausubel (1995) and by Murray (ed.), *Gene Transfer and Expression Protocols* (Humana Press

example within inclusion bodies in prokaryotic hosts. When engineered for export, a supernatant from a culture of the host cell can be used to isolate the exported MMP-25 polypeptide. Typically, the MMP-25 polypeptides used for export in a mammalian cell will include the same export signal that naturally occur with the MMP-25 such as the leader peptide as indicated in Figures 2 and 3. Alternatively, export signals such as leader peptide domains from different exported proteins can be fused to a MMP-25 polypeptide to provide for export in particular cell types.

When expressed in prokaryotic cells, MMP-25 may be isolated from inclusion bodies by a variety of purification procedures. For example, a fraction containing inclusion bodies can be separated from a soluble fraction of disrupted host cells by centrifugation or filtration and the MMP-25-polypeptide can be extracted therefrom using detergents. Optional further purification steps may include binding a sample to MMP-25 antibody bound to a suitable support. In addition, anion or cation exchange resins, gel filtration or affinity, hydrophobic or reverse phase chromatography may be employed in order to purify the protein.

In another alternative, the MMP-25 polypeptide can be isolated from an animal cell such as breast or skin cells in which it is naturally expressed. MMP-25 polypeptides can be purified by any of one or more of the steps common used to purify metalloproteinases generally. In addition or alternatively, the MMP-25 can be excised from a polyacrylamide gel after electrophoresis and identification of the appropriate 54 KD band on the gel as described in Example 5.

Fusion Proteins

The discussion above of isolation of proteins is equally applicable to the isolation of fusion proteins containing a portion of a MMP-25 polypeptide fused to another protein. Fusion proteins are useful for several purposes, including the combining of two or more catalytic functions from separate polypeptide sources, and for raising antibodies to epitopes. For raising antibodies to epitopes, the fusion protein typically contains a peptide epitope of a MMP-25 of at least 8, 10, 15 or 20 amino acids fused to a protein that enhances an immune response to the epitope. A typical protein

for this purpose is KLH. Therefore, another aspect of the present invention provides a non-naturally occurring fusion protein, comprising a first MMP-25 polypeptide segment comprised of at least 8 contiguous amino acids of a MMP-25 polypeptide or variant described above, fused in-frame to a second polypeptide segment. The second polypeptide segment may comprise another portion of the MMP-25 polypeptide that is not naturally adjacent to the first segment, or comprise sequences from a non MMP-25 polypeptide.

Manipulation, Mutation and Expression of Polypeptides

Although various genes (or portions thereof) have been provided herein, it should be understood that within the context of the present invention, reference to one or more of these genes includes derivatives of the genes that are substantially similar to the genes (and, where appropriate, the proteins (including peptides and polypeptides) that are encoded by the genes and their derivatives). As used herein, a nucleotide sequence is deemed to be "substantially similar" if: (a) the nucleotide sequence is derived from the coding region of the above-described genes and includes, for example, portions of the sequence or allelic variations of the sequences discussed above, or alternatively, encodes a molecule which inhibits the binding of MMP-25 to a member of the MMP-25 family, (b) the nucleotide sequence is capable of hybridization to nucleotide sequences of the present invention under moderate, or high stringency as mentioned above. (*also see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, NY, 1989); or (c) the DNA sequences are degenerate as a result of the genetic code in relation to the DNA sequences defined in (a) or (b). Further, the nucleic acid molecule disclosed herein includes both complementary and non-complementary sequences, provided the sequences otherwise meet the criteria set forth herein.

The structure of the proteins encoded by the nucleic acid molecules described herein may be predicted from the primary translation products using the hydrophobicity plot function of, for example, P/C Gene or Intelligenetics Suite

including bacterial, mammalian, yeast or other fungi, viral, insect, or plant cells as described above.

Techniques for transforming fungi are well known in the literature, and have been described, for instance, by Beggs (*ibid.*), Hinnen et al. (*Proc. Natl. Acad. Sci. USA 75*:1929-1933, 1978), Yelton et al. (*Proc. Natl. Acad. Sci. USA 81*:1740-1747, 1984), and Russell (*Nature 301*:167-169, 1983). The genotype of the host cell may contain a genetic defect that is complemented by the selectable marker present on the expression vector. Choice of a particular host and selectable marker is well within the level of ordinary skill in the art.

Protocols for the transformation of yeast are also well known to those of ordinary skill in the art. For example, transformation may be readily accomplished either by preparation of spheroplasts of yeast with DNA (*see* Hinnen et al., *PNAS USA 75*:1929, 1978) or by treatment with alkaline salts such as LiCl (*see* Itoh et al., *J. Bacteriology 153*:163, 1983). Transformation of fungi may also be carried out using polyethylene glycol as described by Cullen et al. (*Bio/Technology 5*:369, 1987).

Viral vectors include those which comprise a promoter that directs the expression of an isolated nucleic acid molecule that encodes a desired protein as described above. A wide variety of promoters may be utilized within the context of the present invention, including for example, promoters such as MoMLV LTR, RSV LTR, Friend MuLV LTR, adenoviral promoter (Ohno et al., *Science 265*:781-784, 1994), neomycin phosphotransferase promoter/enhancer, late parvovirus promoter (Koering et al., *Hum. Gene Therap. 5*:457-463, 1994), Herpes TK promoter, SV40 promoter, metallothionein IIa gene enhancer/promoter, cytomegalovirus immediate early promoter, and the cytomegalovirus immediate late promoter. Within particularly preferred embodiments of the invention, the promoter is a tissue-specific promoter (*see e.g.*, WO 91/02805; EP 0,415,731; and WO 90/07936). Representative examples of suitable tissue specific promoters include neural specific enolase promoter, platelet derived growth factor beta promoter, bone morphogenic protein promoter, human alpha1-chimaerin promoter, synapsin I promoter and synapsin II promoter. In addition to the above-noted promoters, other viral-specific promoters (*e.g.*, retroviral promoters

(including those noted above, as well as others such as HIV promoters), hepatitis, herpes (*e.g.*, EBV), and bacterial, fungal or parasitic (*e.g.*, malarial) -specific promoters may be utilized in order to target a specific cell or tissue which is infected with a virus, bacteria, fungus or parasite.

Mammalian cells suitable for carrying out the present invention include, among others COS, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, and human or mammalian bone marrow stroma. Mammalian expression vectors for use in carrying out the present invention will include a promoter capable of directing the transcription of a cloned gene or cDNA. Preferred promoters include viral promoters and cellular promoters. Bone specific promoters include the bone sialo-protein and the promoter for osteocalcin. Viral promoters include the cytomegalovirus immediate early promoter (Boshart et al., *Cell 41*:521-530, 1985), cytomegalovirus immediate late promoter, SV40 promoter (Subramani et al., *Mol. Cell. Biol. 1*:854-864, 1981), MMTV LTR, RSV LTR, metallothionein-1, adenovirus E1a. Cellular promoters include the mouse metallothionein-1 promoter (Palmiter et al., U.S. Patent No. 4,579,821), a mouse V_K promoter (Bergman et al., *Proc. Natl. Acad. Sci. USA 81*:7041-7045, 1983; Grant et al., *Nucl. Acids Res. 15*:5496, 1987) and a mouse V_H promoter (Loh et al., *Cell 33*:85-93, 1983). The choice of promoter will depend, at least in part, upon the level of expression desired or the recipient cell line to be transfected.

Such expression vectors may also contain a set of RNA splice sites located downstream from the promoter and upstream from the DNA sequence encoding the peptide or protein of interest. Preferred RNA splice sites may be obtained from adenovirus and/or immunoglobulin genes. Also contained in the expression vectors is a polyadenylation signal located downstream of the coding sequence of interest. Suitable polyadenylation signals include the early or late polyadenylation signals from SV40 (Kaufman and Sharp, *ibid.*), the polyadenylation signal from the Adenovirus 5 E1B region and the human growth hormone gene terminator (DeNoto et al., *Nuc. Acids Res. 9*:3719-3730, 1981). The expression vectors may include a noncoding viral leader sequence, such as the Adenovirus 2 tripartite leader, located between the promoter and the RNA splice sites. Preferred vectors may also include enhancer sequences, such as

or V_L domain where these are capable of independently binding antigen with acceptable affinity. Alternatively the V region domain may be dimeric and contain V_H-V_H, V_H-V_L, or V_L-V_L, dimers in which the V_H and V_L chains are non-covalently associated (abbreviated hereinafter as F_V). Where desired, however, the chains may be covalently coupled either directly, for example via a disulphide bond between the two variable domains, or through a linker, for example a peptide linker, to form a single chain domain (abbreviated hereinafter as scF_V).

The variable region domain may be any naturally occurring variable domain or an engineered version thereof. By engineered version is meant a variable region domain which has been created using recombinant DNA engineering techniques. Such engineered versions include those created for example from natural antibody variable regions by insertions, deletions or changes in or to the amino acid sequences of the natural antibodies. Particular examples of this type include those engineered variable region domains containing at least one CDR and optionally one or more framework amino acids from one antibody and the remainder of the variable region domain from a second antibody.

The variable region domain may be covalently attached at a C-terminal amino acid to at least one other antibody domain or a fragment thereof. Thus, for example where a V_H domain is present in the variable region domain this may be linked to an immunoglobulin C_H1 domain or a fragment thereof. Similarly a V_L domain may be linked to a C_K domain or a fragment thereof. In this way for example the antibody may be a Fab fragment wherein the antigen binding domain contains associated V_H and V_L domains covalently linked at their C-termini to a CH1 and C_K domain respectively. The CH1 domain may be extended with further amino acids, for example to provide a hinge region domain as found in a Fab' fragment, or to provide further domains, such as antibody CH2 and CH3 domains.

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction

to synthesize the variable region from RNA of antibody-producing cells (see, for example, Larrick et al., *Methods:A Companion to Methods in Enzymology 2*:106, 1991; Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in *Monoclonal Antibodies:Production, Engineering and Clinical Application*, Ritter et al. (eds.), page 166 (Cambridge University Press 1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies:Principles and Applications*, Birch et al. (eds.), page 137 (Wiley-Liss, Inc. 1995)).

Antibodies for use in the invention may in general be monoclonal (prepared by conventional immunisation and cell fusion procedures) or in the case of fragments, derived therefrom using any suitable standard chemical e.g., reduction or enzymatic cleavage and/or digestion techniques, for example by treatment with pepsin.

More specifically, monoclonal anti-MMP-25 antibodies can be generated utilizing a variety of techniques. Rodent monoclonal antibodies to specific antigens may be obtained by methods known to those skilled in the art (see, for example, Kohler et al., *Nature 256*:495, 1975; and Coligan et al. (eds.), *Current Protocols in Immunology, 1*:2.5.1-2.6.7 (John Wiley & Sons 1991) ["Coligan"]; Picksley et al., "Production of monoclonal antibodies against proteins expressed in *E. coli*," in *DNA Cloning 2:Expression Systems, 2nd Edition*, Glover et al. (eds.), page 93 (Oxford University Press 1995)).

The affinity of a monoclonal antibody or binding partner, as well as inhibition of binding can be readily determined by one of ordinary skill in the art (*see* Scatchard, *Ann. N.Y. Acad. Sci. 51*:660-672, 1949).

Monoclonal antibodies may also be readily generated using techniques described for example, U.S. Patent NOS. 4,902,614, 4,543,439, and 4,411,993 which are incorporated herein by reference; *see also Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Plenum Press, Kennett, McKearn, and Bechtol (eds.), 1980, and *Antibodies:A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988, which are also incorporated herein by reference).

mouse and human variable regions including, among others, primers for V_{Ha}, V_{Hb}, V_{Hc}, V_{Hd}, C_{H1}, V_L and C_L regions. These primers may be utilized to amplify heavy or light chain variable regions, which may then be inserted into vectors such as ImmunoZAP™ H or ImmunoZAP™ L (Stratagene), respectively. These vectors may then be introduced into *E. coli*, yeast, or mammalian-based systems for expression. Utilizing these techniques, large amounts of a single-chain protein containing a fusion of the V_H and V_L domains may be produced (*see* Bird et al., *Science 242*:423-426, 1988). In addition, such techniques may be utilized to change a "murine" antibody to a "human" antibody, without altering the binding specificity of the antibody.

Once suitable antibodies have been obtained, they may be isolated or purified by many techniques well known to those of ordinary skill in the art (*see Antibodies:A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988). Suitable techniques include peptide or protein affinity columns, HPLC or RP-HPLC, purification on protein A or protein G columns, or any combination of these techniques.

In addition, an anti-MMP-25 antibody of the present invention may be derived from a human monoclonal antibody. Human monoclonal antibodies are obtained from transgenic mice that have been engineered to produce specific human antibodies in response to antigenic challenge. In this technique, elements of the human heavy and light chain locus are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci. The transgenic mice can synthesize human antibodies specific for human antigens, and the mice can be used to produce human antibody-secreting hybridomas. Methods for obtaining human antibodies from transgenic mice are described, for example, by Green et al., *Nature Genet. 7*:13, 1994; Lonberg et al., *Nature 368*:856, 1994; and Taylor et al., *Int. Immun. 6*:579, 1994.

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography (see, for example, Coligan at pages 2.7.1-2.7.12 and

pages 2.9.1-2.9.3; Baines et al., "Purification of Immunoglobulin G (IgG)," in *Methods in Molecular Biology, Vol. 10*, pages 79-104 (The Humana Press, Inc. 1992)).

For particular uses, it may be desirable to prepare fragments of anti-MMP-25 antibodies. Such antibody fragments can be obtained, for example, by proteolytic hydrolysis of the antibody. Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies by conventional methods. As an illustration, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment denoted $F(ab')_2$. This fragment can be further cleaved using a thiol reducing agent to produce 3.5S Fab' monovalent fragments. Optionally, the cleavage reaction can be performed using a blocking group for the sulfhydryl groups that result from cleavage of disulfide linkages. As an alternative, an enzymatic cleavage using pepsin produces two monovalent Fab fragments and an Fc fragment directly. These methods are described, for example, by Goldenberg, U.S. Patent No. 4,331,647, Nisonoff et al., *Arch Biochem. Biophys. 89*:230, 1960, Porter, *Biochem. J. 73*:119, 1959, Edelman et al., in *Methods in Enzymology 1*:422 (Academic Press 1967), and by Coligan at pages 2.8.1-2.8.10 and 2.10.-2.10.4.

Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody.

Alternatively, the antibody may be a recombinant or engineered antibody obtained by the use of recombinant DNA techniques involving the manipulation and re-expression of DNA encoding antibody variable and/or constant regions. Such DNA is known and/or is readily available from DNA libraries including for example phage-antibody libraries (see Chiswell, D J and McCafferty, J. Tibtech. 10 80-84 (1992)) or where desired can be synthesised. Standard molecular biology and/or chemistry procedures may be used to sequence and manipulate the DNA, for example, to introduce codons to create cysteine residues, to modify, add or delete other amino acids or domains as desired.

In this practice, one or more replicable expression vectors containing the DNA may be prepared and used to transform an appropriate cell line, e.g., a non-producing myeloma cell line, such as a mouse NSO line or a bacterial, e.g., *E. coli* line, in which production of the antibody will occur. In order to obtain efficient transcription and translation, the DNA sequence in each vector should include appropriate regulatory sequences, particularly a promoter and leader sequence operably linked to the variable domain sequence. Particular methods for producing antibodies in this way are generally well known and routinely used. For example, basic molecular biology procedures are described by Maniatis *et al* (Molecular Cloning, Cold Spring Harbor Laboratory, New York, 1989); DNA sequencing can be performed as described in Sanger et al. (*PNAS 74*:5463 (1977)) and the Amersham International plc sequencing handbook; and site directed mutagenesis can be carried out according to the method of Kramer et al. (*Nucl. Acids Res. 12*:9441 (1984)) and the Anglian Biotechnology Ltd handbook. Additionally, there are numerous publications, detailing techniques suitable for the preparation of antibodies by manipulation of DNA, creation of expression vectors and transformation of appropriate cells, for example as reviewed by Mountain A and Adair, J R in *Biotechnology and Genetic Engineering Reviews* (ed. Tombs, M P, 10, Chapter 1, 1992, Intercept, Andover, UK) and in International Patent Specification No. WO 91/09967.

Where desired, the antibody according to the invention may have one or more effector or reporter molecules attached to it and the invention extends to such modified proteins. The effector or reporter molecules may be attached to the antibody through any available amino acid side-chain, terminal amino acid or, where present carbohydrate functional group located in the antibody, always provided of course that this does not adversely affect the binding properties and eventual usefulness of the molecule. Particular functional groups include, for example any free amino, imino, thiol, hydroxyl, carboxyl or aldehyde group. Attachment of the antibody and the effector and/or reporter molecule(s) may be achieved via such groups and an appropriate functional group in the effector or reporter molecules. The linkage may be direct or indirect, through spacing or bridging groups.

Effector molecules include, for example, antineoplastic agents, toxins (such as enzymatically active toxins of bacterial or plant origin and fragments thereof e.g., ricin and fragments thereof) biologically active proteins, for example enzymes, nucleic acids and fragments thereof, e.g., DNA, RNA and fragments thereof, naturally occurring and synthetic polymers e.g., polysaccharides and polyalkylene polymers such as poly(ethylene glycol) and derivatives thereof, radionuclides, particularly radioiodide, and chelated metals. Suitable reporter groups include chelated metals, fluorescent compounds or compounds which may be detected by NMR or ESR spectroscopy.

Particular antineoplastic agents include cytotoxic and cytostatic agents, for example alkylating agents, such as nitrogen mustards (e.g., chlorambucil, melphalan, mechlorethamine, cyclophosphamide, or uracil mustard) and derivatives thereof, triethylenephosphoramide, triethylenethiophosphor-amide, busulphan, or cisplatin; antimetabolites, such as methotrexate, fluorouracil, floxuridine, cytarabine, mercaptopurine, thioguanine, fluoroacetic acid or fluorocitric acid, antibiotics, such as bleomycins (e.g., bleomycin sulphate), doxorubicin, daunorubicin, mitomycins (e.g., mitomycin C), actinomycins (e.g., dactinomycin) plicamycin, calichaemicin and derivatives thereof, or esperamicin and derivatives thereof; mitotic inhibitors, such as etoposide, vincristine or vinblastine and derivatives thereof; alkaloids, such as ellipticine; polyols such as taxicin-I or taxicin-II; hormones, such as androgens (e.g., dromostanolone or testolactone), progestins (e.g., megestrol acetate or medroxyprogesterone acetate), estrogens (e.g., dimethylstilbestrol diphosphate, polyestradiol phosphate or estramustine phosphate) or antiestrogens (e.g., tamoxifen); anthraquinones, such as mitoxantrone, ureas, such as hydroxyurea; hydrazines, such as procarbazine; or imidazoles, such as dacarbazine.

Particularly useful effector groups are calichaemicin and derivatives thereof (see for example South African Patent Specifications NOS. 85/8794, 88/8127 and 90/2839).

Chelated metals include chelates of di-or tripositive metals having a coordination number from 2 to 8 inclusive. Particular examples of such metals include technetium (Tc), rhenium (Re), cobalt (Co), copper (Cu), gold (Au), silver (Ag), lead (Pb),

bismuth (Bi), indium (In), gallium (Ga), yttrium (Y), terbium (Tb), gadolinium (Gd), and scandium (Sc). In general the metal is preferably a radionuclide. Particular radionuclides include ^{99m}Tc, ^{186}Re, ^{188}Re, ^{58}Co, ^{60}Co, ^{67}Cu, ^{195}Au, ^{199}Au, ^{110}Ag, ^{203}Pb, ^{206}Bi, ^{207}Bi, ^{111}In, ^{67}Ga, ^{68}Ga, ^{88}Y, ^{90}Y, ^{160}Tb, ^{153}Gd and ^{47}Sc.

The chelated metal may be for example one of the above types of metal chelated with any suitable polydentate chelating agent, for example acyclic or cyclic polyamines, polyethers (e.g., crown ethers and derivatives thereof); polyamides; porphyrins; and carbocyclic derivatives.

In general, the type of chelating agent will depend on the metal in use. One particularly useful group of chelating agents in conjugates according to the invention, however, are acyclic and cyclic polyamines, especially polyaminocarboxylic acids, for example diethylenetriaminepentaacetic acid and derivatives thereof, and macrocyclic amines, e.g., cyclic tri-aza and tetra-aza derivatives (for example as described in International Patent Specification No. WO 92/22583); and polyamides, especially desferrioxamine and derivatives thereof.

Thus for example, when it is desired to use a thiol group in the antibody as the point of attachment this may be achieved through reaction with a thiol reactive group present in the effector or reporter molecule. Examples of such groups include an á-halocarboxylic acid or ester, e.g., iodoacetamide, an imide, e.g., maleimide, a vinyl sulphone, or a disulphide. These and other suitable linking procedures are generally and more particularly described in International Patent Specifications NOS. WO 93/06231, WO 92/22583, WO 90/091195 and WO 89/01476.

RIBOZYMES AND ANTISENSE MOLECULES

In another aspect, the nucleic acid sequences of the present invention provide for nucleic acids useful for modulating or inhibiting the expression of a MMP-25 polypeptide in a cell. More specifically, the invention provides for a ribozyme that cleaves RNA encoding the aforementioned MMP-25 polypeptides. Also included is a nucleic acid molecule comprising a sequence that encodes such a ribozyme and a vector comprising the nucleic acid molecule. In a similar aspect, the invention provides

antisense nucleic acid molecule comprising a sequence that is antisense to a portion of the MMP-25 nucleic acids described herein. Also included are a vector comprising the antisense molecule, and vectors wherein the aforementioned ribozyme or antisense nucleic acid is operably linked to a promoter. Typical embodiments of these vectors are selected from the group consisting of plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors. Host cells comprising the above vectors are also included.

Antisense oligonucleotide molecules are provided which specifically inhibit expression of MMP-25 nucleic acid sequences (*see generally*, Hirashima et al. in *Molecular Biology of RNA:New Perspectives* (M. Inouye and B. S. Dudock, eds., 1987 Academic Press, San Diego, p. 401); *Oligonucleotides:Antisense Inhibitors of Gene Expression* (J.S. Cohen, ed., 1989 MacMillan Press, London); Stein and Cheng, *Science 261*:1004-1012, 1993; WO 95/10607; U.S. Patent No. 5,359,051; WO 92/06693; and EP-A2-612844). Briefly, such molecules are constructed such that they are complementary to, and able to form Watson-Crick base pairs with, a region of transcribed MMP-25 mRNA sequence. The resultant double-stranded nucleic acid interferes with subsequent processing of the mRNA, thereby preventing protein synthesis (Example 6).

Ribozymes are provided which are capable of inhibiting expression of MMP-25 RNA. As used herein, "ribozymes" are intended to include RNA molecules that contain anti-sense sequences for specific recognition, and an RNA-cleaving enzymatic activity. The catalytic strand cleaves a specific site in a target RNA at greater than stoichiometric concentration. A wide variety of ribozymes may be utilized within the context of the present invention, including for example, the hammerhead ribozyme (for example, as described by Forster and Symons, *Cell 48*:211-220, 1987; Haseloff and Gerlach, *Nature 328*:596-600, 1988; Walbot and Bruening, *Nature 334*:196, 1988; Haseloff and Gerlach, *Nature 334*:585, 1988); the hairpin ribozyme (for example, as described by Haseloff et al., U.S. Patent No. 5,254,678, issued October 19, 1993 and Hempel et al., European Patent Publication No. 0 360 257, published March 26, 1990); and *Tetrahymena* ribosomal RNA-based ribozymes (see Cech et al.,

hydroxyamino)-2R-isobutyl-3S-(thiopen-2-ylthiomethyl)-succinyl-L-phenylalanine-N-methylamidecarboxyalkylamino-based compounds such as N-1-(R)-carboxy-3-(1,3-dihydro-2H-benzfisoindol-2-yl)propyl-N',N'-dime thyl-L-leucinamide, trifluoroacetate (*J. Med Chem. 36*:4030-4039, 1993); marimastat (BB-2516); N-chlorotaurine; eicosapentaenoic acid; matlystatin-B; actinonin (3-1-2-(hydroxymethyl)-1-pyrolidinylcarbamoyl-octanohydroxamic acid); N-phosphonalkyl dipeptides such as N-N-((R)-1-phosphonopropyl)-(S)-leucyl-(S)-phenylalanine-N-methylamide (*J. Med. Chem. 37*:158-169, 1994); peptidyl hydroxamic acids such as pNH.sub.2 -Bz-Gly-Pro-D-Leu-D-Ala-NHOH (*Biophys. Biochem. Res. Comm. 199*:1442-1446, 1994); Ro-31-7467, also known as 2-(5-bromo-2,3-dihydro-6-hydroxy-1,3-dioxo-1 H benzdelisoquinolin-2-yl)met hyl(hydroxy)-phosphinyl-N-(2-oxo-3-azacyclotridecanyl)-4-methylvaleramid e; CT1166, also known as N1N2-(morpholinosulphonylamino)-ethyl-3-cyclohexyl-2-(S)-propanamidyl -N4-hydroxy-2-(R)-3-(4-methylphenyl)propyl-succinamide (*Biochem. J. 308*:167-175, 1995); bromocyclic-adenosine monophosphate; protocatechuic aldehyde (3,4-dihydroxybenzaldehyde); estramustine (estradiol-3-bis(2-chloroethyl)carbamate); tetracycline (4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydro xy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide); minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline); methacycline (6-methylene oxytetracycline); and doxycycline (.alpha.-6-deoxy-5-hydroxytetracycline). Preferably, the inhibitor of an MMP includes an inhibitor other than an unsaturated fatty acid such as eicosapentaenoic acid.

Other inhibitors include tetracyline derivatives described in U.S. Patent No. 5,837,696 to Golub et al., which are disclosed to be useful for inhibiting MMP activity in cancer cells. Other classes of MMP inhibitors include the aryl-sulfonyl and related compounds described in U.S. Patent No. 5,866,587 to de Nanteuil et al. Others include those described by Gowravaram, *J. Med. Chem. 38*:2570-2581 (1995), which describes the development of a series of hydroxamates that inhibit MMPs and mentions thiols, phosphonates, phosphinates, phosphoramidates and N-carboxy alkyls as known MMP inhibitors. This reference indicates that MMP inhibitors typically may include a moiety that chelates zinc and a peptidic fragment that binds a subset of the specificity

pockets of MMPs. Hodgson, *Biotechnology 13*:554-557 1995 (1995), reviews the clinical status of several MMP inhibitors, including Galardin, Batimastat, and Marimastat. Further MMP inhibitors include butanediamide (Conway et al., *J. Exp. Med. 182*:449-457 (1995)), TIMPs (Mauch et al., *Arch. Dermatol. Res. 287*:107-114 (1994)), and retinoids (Fanjul et al., *Nature 372*:107-111 (1994); Nicholson et al., *EMBO Journal 9*(13):4443-4454 (1990); and Bailly, C. et al., *J. Investig. Derm. 94*(1):47-51 (1990)).

Indirect inhibitors may also be used, which include for example, inhibitors of transcription factors such as AP-1 NF-kappa B, and the cascade of factors regulated thereby which are involved in MMP regulation as mentioned in U.S. Patent No. 5,837,224. Hill, P. A. et al., *Biochem. J. 308*:167-175 (1995), describes two MMP inhibitors, CT1166 and RO317467, that may regulate MMP transcription factors.

The inhibitor may inhibit multiple types of MMPs, for example, MMP-1 (interstitial collagenase), MMP-2 (72 kD collagenase), MMP-3 (stromelysin), MMP-4 (telopeptidase), MMP-5 (collagen endopeptidase), MMP-6 (acid metalloproteinase), MMP-7 (uterine metalloproteinase), MMP-8 (neutrophil collagenase), and/or MMP-9 (92 kD collagenase). Inhibitors are preferably selected which preferentially inhibit MMP-25 over the non-type 25 MMPs.

In another embodiment of the method, the inhibitor agent is a nucleic acid or product encoded thereby which is delivered and expressed in the cell by a vector. More specifically, this embodiment of inhibiting the expression of a metalloproteinase includes the steps of administering to the cell a vector comprising a nucleic acid means for inhibiting expression of a MMP-25 polypeptide. Embodiments of this method include those where the nucleic acid means comprises a ribozyme that cleaves an RNA encoding the MMP-25 polypeptide or comprises a molecule that is antisense to a portion of an RNA encoding the MMP-25 polypeptide. In other embodiments of this method, the nucleic acid means is a non-functional variant of a MMP-25 polypeptide. Particularly useful non-functional variants include variants of the amino acid sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6; (b) an amino acid sequence having at least 50% identity to the polypeptide of (a) or (b);

EXAMPLES

EXAMPLE 1

CLONING OF A LONG MMP-25 cDNA - MMP-25(*l*)

A first matrix metalloproteinase, herein designated as MMP-25(*l*), was identified. The polynucleotide encodes a protein comprising the conserved peptide sequences LVAAHELGHXLGLXHSXXXXAXMSSSY (SEQ ID NO:7) and HGDXXPFDGXXXXLAHAFXPGXGXGGDXHPDXDEXWT (SEQ ID NO:8) where X is any amino acid. These conserved peptide sequences represent a consensus for MMP polypeptides as determined by aligning protein sequences of several MMP family members using a multiple sequence alignment program. The consensus sequence is representative of conserved amino acid residues within two separate Zn-binding domains, both of which are ordinarily present on MMPs.

The first MMP sequence identified comprised 833 bp (SEQ ID NO:1). To obtain a full-length cDNA sequence for the novel MMP, a mammary gland cDNA expression library was screened by amplification using RACE reactions with unique sequence primers deduced from the 833 bp sequence in combination with primers that bind to 5' and 3' vector sequences adjacent to the ends of cloned inserts. In particular, the vector primer AP1 (Clontech, Palo Alto, CA) was used with one of the following primers from the candidate 833 bp sequence to amplify the 5' sequences:

GSP1: 8563 TGATATCATAATAGATCCTCCATAGGTGCC SEQ ID NO:9

GSP 2: 8564 TTCCTTAGGCAGACCTCCATAGATGGACTGG SEQ ID NO:10

Similarly, the vector primer AP2 (Clontech, Palo Alto, CA) was used with one of the following primers from the candidate 833 bp sequence to amplify the 3' sequences:

GSP3: 7433 CCTAAGGAACCTGCTAAGCCAAAGGAA SEQ ID NO:11

GSP4: 7560 CCGCAGAGAAGTAATGTTCTTTAAA SEQ ID NO:12

Typical RACE reaction conditions were used to amplify cloned sequences, e.g., 35 cycles of a 30 second denaturation followed by a 4 minute extension at between 68 and 72°C. Amplified nucleic acids were isolated and sequenced.

Using the above method, a novel sequence of 1833 bp in length (SEQ ID NO:5) with an open reading frame of 1539 bp (position 12 to 1550 of SEQ ID NO:5) was identified (*see*, Figure 2). SEQ ID NO:5 also contained a poly-A tail with a polyadenylation sequence (ATTAAA) located 24 bp upstream (*see*, Figure 2), indicative of a true cDNA.

EXAMPLE 2

IDENTIFICATION OF MMP-25 (*s*)

A second novel metalloproteinase sequence, herein designated MMP-25(*s*), was also identified by cDNA library screening using RACE reactions as described in EXAMPLE 1. The nucleotide sequence encoding MMP-25(*s*) is shown in SEQ ID NO:3 and the encoded amino sequence encoded is shown in SEQ ID NO:4. The nucleotide sequence of MMP-25(s) was identical to the sequence for MMP-25(l) except in having a deletion of 129 nucleotides corresponding to 43 amino acids. The deleted sequence in the shorter version of MMP-25 is unique among metalloproteinases: while the encoded protein contains the first Zn-binding domain, it lacks the second Zn/Ca-binding domain typical for other members of the matrix metalloproteinase family as illustrated in Figure 3.

EXAMPLE 3

TISSUE EXPRESSION PATTERNS OF MMP-25 SEQUENCES

The MMP nucleic acids and polypeptides of the present invention have a unique pattern of tissue expression in human tissue as illustrated in Figure 4. RT-PCR reactions using reverse transcriptase were performed on RNA samples isolated from a tissue panel from 36 normal tissues. Figure 4 illustrates that both the long and short

variants of MMP-25 were expressed in fetal skin and mammary glands after 35 cycles of amplification, but were poorly detected in other tissues.

The expression in skin tissue is localized in skin follicle cells as illustrated by in situ hybridization results illustrated in Figure 4. Briefly, fetal skin samples fixed in 4% paraformaldehyde, embedded in paraffin and cut into 5 μm sections were obtained from Biochain Inc. (San Leandro, CA) Sections were deparaffinized with xylene and rehydrated using standard procedures. Single-stranded digoxigenin-containing (Roche Molecular Biochemicals (Indianapolis, IN) sense and antisense riboprobes were made in vitro using linear templates of MMP-25 DNA and T7 RNA polymerase. Reaction yield and integrity were assessed by gel electrophoresis.

Tissue sections were washed in 10 mM Tris (pH 7.5), 150 mM NaCl for 5 min, followed by a 2 hr blocking step using normal sheep serum (3% final) Sigma, St. Louis MO) and 0.035 Triton in 10 mM Tris (pH 7.5) 150 mM NaCl. The slides were incubated with alkaline phosphatase-conjugated anti-DIG antibody (Roche Molecular Biochemicals) at a 1/200 dilution overnight at 4°C in 10 mM Tris (pH 7.5), 150 mM NaCl supplemented with 1% normal sheep serum. Reference sequential-sections were stained with hemotoxylin and mounted for visualization by light microscopy.

The in situ hybridization results revealed that MMP-25 was expressed in the inner root sheath layer of the hair follicle as shown in Figure 5. The cell layer within the inner root sheath, the Henle layer, was further defined as a particular cell type for MMPP25 mRNA expression in skin. The particular localization of MMP-25 expression in inner root sheath of hair follicles indicates that control of the expression of the MMP-25 sub-family of metalloproteinases is involved in the regulation of hair growth.

EXAMPLE 4

CHROMOSOMAL LOCATION FOR HUMAN MMP-25

A chromosomal location of MMP-25 was determined using two primers unique to MMP-25 nucleic acids. The primers DMO 7560 (SEQ ID NO:13) and DMO 8563 (SEQ ID NO:14) were used to screen a G3 radiation hybrid panel to map the

location of MMP-25. MMP-25 maps to chromosome 11q22, a region where several other MMPs including MMP1, MMP3, MMP7, MMP8, MMP10, MMP12, and MMP13, have been previously mapped.

EXAMPLE 5

METHOD OF MODULATING HAIR GROWTH

In one practice of an improved method of modulating hair growth, a dermatologically acceptable composition comprising a known MMP inhibitor is applied in an amount that inhibits the activity of MMP-25 to a greater extent than it inhibits the activity of other MMPs. Such an inhibitor is preferably incorporated into a topical composition adapted for application to the skin.

The amount of inhibitor that preferentially inhibits MMP-25 is determined by assessing the level of reduced MMP catalytic activity against a panel of known MMP enzymes. The zymography procedure described in U.S. Patent No. 5,962,466 is used to assess relative catalytic activity of the 54 KD MMP-25(l) of the present invention in comparison to the activity of the 72kD MMP-2 and 92 kD MMP-9 present in extracts of skin tissue.

Briefly, hair follicles are removed from mammalian skin and homogenized in a non-denaturing buffer, for example a buffer containing 25 mM Tris, H 7.5 and 50 mM sucrose. The samples are prepared for SDS gel electrophoresis and separated on an SDS polyacrylamide gel containing a suitable amount of MMP substrate (e.g., 0.1% gelatin) incorporated therein. The separated proteins are renatured within the gel by incubation with a suitable renaturing buffer such as 2.5% Triton X-100, and renatured in the presence of a buffer containing test amounts of selected MMP inhibitors, for example 0.01 - 10 mM tetracycline, minocyclene, doxycycline, methacycline or 1,10-phenanthroline. The gel is developed in suitable buffer for detecting MMP activity, such as 10 mM Tris base, 40 mM Tris HCl, 200 mM NaCl, 5 mM $CaCl_2$ and 0.02% Brij 35.

The relative levels of MMP activity and level of inhibition are assessed by detecting the presence and size of "ghost bands" corresponding to the positions of

antisense oligonucleotide results in a 25% change in either instance compared to the control scrambled oligonucleotide.

In providing the forgoing description of the invention, citation has been made to several references that will aid in the understanding or practice thereof. All such references are incorporated by reference herein.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. An isolated nucleic acid molecule consisting essentially of a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence according to SEQ ID NOs:1, 3 and 5

(b) a nucleotide sequence having at least 85% identity to the nucleotide sequence according to SEQ ID NOs:1, 3 and 5;

(c) complements of a sequences according to SEQ ID NO:1, 3 and 5; and

(d) sequences that hybridizes to a sequence according to SEQ ID NO:1, 3 and 5 under conditions of normal stringency.

2. A polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence according to SEQ ID NOs:2, 4 and 6;

(b) an amino acid sequence having at least 90% identity to the amino acid sequence according to SEQ ID NOs:2, 4 and 6;

(c) a nucleotide sequence encoded by a nucleic acid molecule according to claim 1; and

(d) a nucleotide sequence having at least 85% identity to the nucleotide sequence encoded by a nucleic acid molecule according to claim 1; and

(e) an amino acid sequence encoded by a nucleic acid that hybridizes under conditions of normal stringency to the nucleic acid molecule according to claim 1.

3. A method of identifying a nucleic acid molecule encoding all or a part of a metalloproteinase, comprising:

(1) hybridizing a nucleic acid molecule sample to the nucleic acid molecule according to claim 1 and;

(b) a polypeptide comprising a first matrix metalloproteinase Zn-binding domain with the proviso that the polypeptide lacks a second matrix metalloproteinase Zn-binding domain; and

(c) an amino acid sequence encoded by a nucleic acid that hybridizes under conditions of high stringency to a nucleic acid molecule according to claim 1.

19. The method of claim 17, wherein said nucleic acid molecule encodes a ribozyme that cleaves a RNA encoding the matrix metalloproteinase -25 polypeptide.

20. The method of claim 17, wherein said nucleic acid molecule contains a sequence that is antisense to a portion of a RNA encoding the matrix metalloproteinase -25 polypeptide.

21. A method of modulating hair growth in a mammal, comprising applying a dermatologically acceptable composition comprising an inhibitor of a matrix metalloproteinase, with the proviso that the applied composition reduces the catalytic activity of a type 25 matrix metalloproteinase to a greater extent than it reduces the catalytic activity of at least one non-type 25 matrix metalloproteinase.

22. A polypeptide according to claim 2, wherein said polypeptide has a first matrix metalloproteinase Zn-binding domain and lacks a second matrix metalloproteinase Zn-binding domain.

23. The polypeptide of claim 22, wherein said polypeptide exhibits a catalytic activity of a matrix metalloproteinase.

24. The polypeptide of claim 22, wherein said polypeptide lacks a catalytic activity of a matrix metalloproteinase.

Initial assembled sequence
[Strand]

```
1    AGAAAATACC CACTTTCTCA GGATGATATC AATGGAATCC AGTCCATCTA TGGAGGTCTG
61   CCTAAGGAAC CTGCTAAGCC AAAGGAACCC ACTATACCCC ATGCCTGTGA CCCTGACTTG
121  ACTTTTGACG CTATCACAAC TTTCCGCAGA GAAGTAATGT TCTTTAAAGG CAGGCACCTA
181  TGGAGGATCT ATTATGATAT CACGGATGTT GAGTTTGAAT TAATTGCTTC ATTCTGGCCA
241  TCTCTGCCAG CTGATCTGCA AGCTGCATAC GAGAACCCCA GAGATAAGAT TCTGGTTTTT
301  AAAGATGAAA ACTTCTGGAT GATCAGAGGA TATGCTGTCT TGCCAGATTA TCCCAAATCC
361  ATCCATACAT TAGGTTTTCC AGGACGTGTG AAGAAAATAG ATGCAGCCGT CTGTGATAAG
421  ACCACAAGAA AAACCTACTT CTTTGTGGGC ATTTGGTGCT GGAGGTTTGA TGAAATGACC
481  CAAACCATGG ACAAAGGGTT CCCGCAGAGA GTGGTAAAAC ACTTTCCTGG AATCAGTATC
541  CGTGTTGATG CTGCTTTCCA GTACAAAGGA TTCTTCTTTT TCAGCCGTGG ATCAACGCAA
601  TTTGAATACG ACATTAAGAC AAAGAATATT ACCCGAATCA TGAGAACTAA TACTTGGTTT
661  CAATGCAAAG AACCAAAGAA CTCCTCATTT GGTTTTGATA TCAACAAGGA AAAAGCACAT
721  TCAGGAGGCA TAAAGATATT GTATCATAAG AGTTTAAGCT TGTTTATTTT TGGTATTGTT
781  CATTTGCTGA AAAACACTTC TATTTATCAA TAAATTCATA GACCTAAAAT AAA
```

Fig. 1

```
gaaagagagg a atg aag cgc ctt ctg ctt ctg ttt ttg ttc ttt ata aca   50
              Met Lys Arg Leu Leu Leu Leu Phe Leu Phe Phe Ile Thr
               1               5                  10

ttt tct tct gca ttt ccc tta gtc cgg atg atg gaa aat gaa gaa aat   98
Phe Ser Ser Ala Phe Pro Leu Val Arg Met Met Glu Asn Glu Glu Asn
    15                  20                  25

gtg caa ctg gct cag gca tat ctc aac cag ttc tac tct ctt gaa ata  146
Val Gln Leu Ala Gln Ala Tyr Leu Asn Gln Phe Tyr Ser Leu Glu Ile
30                  35                  40                  45

gaa ggg aat cat ctt gtt caa agc aag aat agg agt ctc ata gat gac  194
Glu Gly Asn His Leu Val Gln Ser Lys Asn Arg Ser Leu Ile Asp Asp
                50                  55                  60

aaa att cgg gaa atg caa gca ttt ttt gga ttg aca gtg act gga aga  242
Lys Ile Arg Glu Met Gln Ala Phe Phe Gly Leu Thr Val Thr Gly Arg
            65                  70                  75

ctg gac tca aac acc ctt gag atc atg aag aca ccc agg tgt ggg gtg  290
Leu Asp Ser Asn Thr Leu Glu Ile Met Lys Thr Pro Arg Cys Gly Val
        80                  85                  90

cct gat gtg ggc cag tat ggc tac acc ctc cct ggg tgg aga aaa tac  338
Pro Asp Val Gly Gln Tyr Gly Tyr Thr Leu Pro Gly Trp Arg Lys Tyr
    95                  100                 105

aac ctc acc tac aga ata ata aac tat act ccg gat atg gca cga gct  386
Asn Leu Thr Tyr Arg Ile Ile Asn Tyr Thr Pro Asp Met Ala Arg Ala
110                 115                 120                 125

gct gtg gat gag gct atc caa gaa ggt tta gaa gtg tgg agc aaa gtc  434
Ala Val Asp Glu Ala Ile Gln Glu Gly Leu Glu Val Trp Ser Lys Val
            130                 135                 140

act cca cta aaa ttc acc aag att tca aag ggg att gca gac atc atg  482
Thr Pro Leu Lys Phe Thr Lys Ile Ser Lys Gly Ile Ala Asp Ile Met
        145                 150                 155
```

Fig. 2A

```
att gcc ttt agg act cga gtc cat ggt cgg tgt cct cgc tat ttt gat   530
Ile Ala Phe Arg Thr Arg Val His Gly Arg Cys Pro Arg Tyr Phe Asp
        160                 165                 170

ggt ccc ttg gga gtt ctt ggc cat gcc ttt cct cct ggt ccg ggt ctg   578
Gly Pro Leu Gly Val Leu Gly His Ala Phe Pro Pro Gly Pro Gly Leu
    175                 180                 185

ggt ggt gac act cat ttt gat gag gat gaa aac tgg acc aag gat gga   626
Gly Gly Asp Thr His Phe Asp Glu Asp Glu Asn Trp Thr Lys Asp Gly
190                 195                 200                 205

gca gga ttc aac ttg ttt ctt gtg gct gct cat gaa ttt ggt cat gca   674
Ala Gly Phe Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ala
            210                 215                 220

ctg ggg ctc tct cac tcc aat gat caa aca gcc ttg atg ttc cca aat   722
Leu Gly Leu Ser His Ser Asn Asp Gln Thr Ala Leu Met Phe Pro Asn
        225                 230                 235

tat gtc tcc ctg gat ccc aga aaa tac cca ctt tct cag gat gat atc   770
Tyr Val Ser Leu Asp Pro Arg Lys Tyr Pro Leu Ser Gln Asp Asp Ile
    240                 245                 250

aat gga atc cag tcc atc tat gga ggt ctg cct aag gaa cct gct aag   818
Asn Gly Ile Gln Ser Ile Tyr Gly Gly Leu Pro Lys Glu Pro Ala Lys
255                 260                 265

cca aag gaa ccc act ata ccc cat gcc tgt gac cct gac ttg act ttt   866
Pro Lys Glu Pro Thr Ile Pro His Ala Cys Asp Pro Asp Leu Thr Phe
270                 275                 280                 285

gac gct atc aca act ttc cgc aga gaa gta atg ttc ttt aaa ggc agg   914
Asp Ala Ile Thr Thr Phe Arg Arg Glu Val Met Phe Phe Lys Gly Arg
            290                 295                 300

cac cta tgg agg atc tat tat gat atc acg gat gtt gag ttt gaa tta   962
His Leu Trp Arg Ile Tyr Tyr Asp Ile Thr Asp Val Glu Phe Glu Leu
        305                 310                 315
```

Fig. 2B

```
att gct tca ttc tgg cca tct ctg cca gct gat ctg caa gct gca tac 1010
Ile Ala Ser Phe Trp Pro Ser Leu Pro Ala Asp Leu Gln Ala Ala Tyr
        320                 325                 330

gag aac ccc aga gat aag att ctg gtt ttt aaa gat gaa aac ttc tgg 1058
Glu Asn Pro Arg Asp Lys Ile Leu Val Phe Lys Asp Glu Asn Phe Trp
    335                 340                 345

atg atc aga gga tat gct gtc ttg cca gat tat ccc aaa tcc atc cat 1106
Met Ile Arg Gly Tyr Ala Val Leu Pro Asp Tyr Pro Lys Ser Ile His
350                 355                 360                 365

aca tta ggt ttt cca gga cgt gtg aag aaa ata gat gca gcc gtc tgt 1154
Thr Leu Gly Phe Pro Gly Arg Val Lys Lys Ile Asp Ala Ala Val Cys
                370                 375                 380

gat aag acc aca aga aaa acc tac ttc ttt gtg ggc att tgg tgc tgg 1202
Asp Lys Thr Thr Arg Lys Thr Tyr Phe Phe Val Gly Ile Trp Cys Trp
            385                 390                 395

agg ttt gat gaa atg acc caa acc atg gac aaa ggg ttc ccg cag aga 1250
Arg Phe Asp Glu Met Thr Gln Thr Met Asp Lys Gly Phe Pro Gln Arg
        400                 405                 410

gtg gta aaa cac ttt cct gga atc agt atc cgt gtt gat gct gct ttc 1298
Val Val Lys His Phe Pro Gly Ile Ser Ile Arg Val Asp Ala Ala Phe
    415                 420                 425

cag tac aaa gga ttc ttc ttt ttc agc cgt gga tca acg caa ttt gaa 1346
Gln Tyr Lys Gly Phe Phe Phe Phe Ser Arg Gly Ser Thr Gln Phe Glu
430                 435                 440                 445

tac gac att aag aca aag aat att acc cga atc atg aga act aat act 1394
Tyr Asp Ile Lys Thr Lys Asn Ile Thr Arg Ile Met Arg Thr Asn Thr
                450                 455                 460

tgg ttt caa tgc aaa gaa cca aag aac tcc tca ttt ggt ttt gat atc 1442
Trp Phe Gln Cys Lys Glu Pro Lys Asn Ser Ser Phe Gly Phe Asp Ile
            465                 470                 475
```

Fig. 2C

```
aac aag gaa aaa gca cat tca gga ggc ata aag ata ttg tat cat aag  1490
Asn Lys Glu Lys Ala His Ser Gly Gly Ile Lys Ile Leu Tyr His Lys
        480                 485                 490

agt tta agc ttg ttt att ttt ggt att gtt cat ttg ctg aaa aac act  1538
Ser Leu Ser Leu Phe Ile Phe Gly Ile Val His Leu Leu Lys Asn Thr
    495                 500                 505

tct att tat caa taaattcata gacctaaaat aaacctcaac aggtctttta      1590
Ser Ile Tyr Gln
510

atataaattc tgcttcaaaa tagaataaaa ccattcttta acaacaagtt gctggtccta  1650
gttctaaata tccaaattca atggccattt tgagctgcct gattctttta ataggaagtt  1710
attatgtaga aacaaaaatc tctgactgta ctttaagcct atttcatgct ttgtggactt  1770
ggagaagaca tgtcttataa ctgaatactg aaacatttat taaaccaatc tttagcattc  1830
tg                                                                 1832
```

Fig. 2D

```
176  ..V.QEVPYEDIRLRRQKE....VL.ASGF..DS-----SP-....TG.F.A..YF.....-.........A..P..FSSTDL----------  MTM2HUM.PRO
164  ..T.EEVPYSELENGK-RDV..P.I.ASGF..DS-----SP-....EG.F.A..YF.....-I.........S..P..LGNPNH----------  MTM3HUM.PRO
 88  ..N.HE-----VA---GST...Q.D.SKAD.NDG-----YP-....G.TVA...F..HHHTA.....D..A..FRSSD----------  MMP 17P
141  ..T.QEV--------QA.A...RLS.HG.QSSY.-----SNT....GR..A..DI.EL----.SV.....F..EGT----------  MMP 18P
150  ...N...RL---------HD.........S.GIKE..DF-----YP-....S.L.A.........N-Y...A...D..T..SSSK----------  MMP 20P
 78  G.T.HE-----VDSPQGQEP..L.D.ARAF.QDS-----YP-....LG.T.A...F..EHPIS.....DE.T..FGSKA----------  MMP 21P
126  .FS.REVA---------PEQPS.LR.G.YPIN.TD.LVSALHHC.....T.E.A...F.PH----.GI....DS.Y.VLGPTR----------  MMP 22P
156  ..R.SR.----------HD.E.....N.GRWE..DG-----YP-....KD.L.A...A..T..-V...S....D..L...LGEGQVVRVKYGNADG  GELAHUM.PRO
153  ..T...RV---------YSRD...V.Q.GVAE..DG-----YP-....KD.L.A.........-IQ..A...D..L.SLGKGVVVPTRFGNADG  GELBHUM.PRO

206  ----------------------------------------------------------------------  contig 355 long
263  ----------------------------------------------------------------------  contig 355 short
208  ----------------------------------------------------------------------  COLL1HUM.PRO
207  ----------------------------------------------------------------------  COLL2HUM.PRO
212  ----------------------------------------------------------------------  COLL3HUM.PRO
208  -----FLYA------------------------------------------------------------  MATRHUM.PRO
208  ----------------------------------------------------------------------  METAHUM.PRO
208  ----------------------------------------------------------------------  STO1HUM.PRO
207  ----------------------------------------------------------------------  STO2HUM.PRO
203  ----------------------------------------------------------------------  STO3HUM.PRO
228  ----------------------------------------------------------------------  MTM1HUM.PRO
248  ----------------------------------------------------------------------  MTM2HUM.PRO
235  ----------------------------------------------------------------------  MTM3HUM.PRO
152  ----------------------------------------------------------------------  MMP 17P
201  ----------------------------------------------------------YR----------  MMP 18P
212  ----------------------------------------------------------------------  MMP 20P
145  ----------------------------------------------------------------------  MMP 21P
```

Fig. 3C

```
194 ----------------------------------------------------------YSW----  MMP 22P
231 EYCKFPFLFNGKEYNSCTDTGRSDGFLWCSTTYNFEKDGKYGFCPHEALFTMGGNAEGQPCKFPFRFQGTSYDSCTTEGRTDGYRWCGTT  GELAHUM.PRO
228 AACHFPFIFEGRSYSACTTDGRSDGLPWCSTTANYDTDDRFGFCPSERLYTRDGNADGKPCQFPFIFQGQSYSACTTDGRSDGYRWCATT  GELBHUM.PRO

207 ----------------------------------------GFNLFLVAAHEFGHAL  contig 355 long
164 ----------------------------------------.....  contig 355 short
209 ----------------------------------------EY..HR.....L..S.  COLL1HUM.PRO
208 ----------------------------------------NY.....S.  COLL2HUM.PRO
213 ----------------------------------------Y.....S.  COLL3HUM.PRO
212 ----------------------------------------T..L..S.  MATRHUM.PRO
209 ----------------------------------------T....T.V..I..S.  METAHUM.PRO
209 ----------------------------------------T.....I..S.  STO1HUM.PRO
208 ----------------------------------------T.....L..S.  STO2HUM.PRO
204 ----------------------------------------DQ.TD.LQ.....V.  STO3HUM.PRO
229 ----------------------------------------N.NDI.....V..L.....  MTM1HUM.PRO
249 ----------------------------------------H.N.....V..L.....  MTM2HUM.PRO
236 ----------------------------------------D.ND.....V..L.....  MTM3HUM.PRO
153 ----------------------------------------AH.MD..A..V.....I  MMP 17P
203 ----------------------------------------V..RII.....V.....  MMP 18P
213 ----------------------------------------Y.....S.  MMP 20P
146 ----------------------------------------SQQLE-----Q.LAGG-  MMP 21P
197 ----------------------------KKGVW----------LTD.VH.....I.....  MMP 22P
321 EDYDRDKKYGFCPETAMSTV-GGNSEGAPCVFPFTFLGNKYESCTSAGRSDGKMWCATTANYDDDRKWGFCPDQ.YS.....M  GELAHUM.PRO
318 ANYDRDKLFGFCPTRADSTVMGGNSAGELCVFPFTFLGKEYSTCTSEGRGDGRLWCATTSNFDSDKKWGFCPDQ.YS.....  GELBHUM.PRO
```

Fig. 3D

```
                Zn++ binding domain
223 GLSHSNDQTALMFPNYVS-L-DPRKYPLS--QDDINGIQSIYGG-------LPKEPAKPKEPTIP---------- contig 355 long
180 ..........  ..........  ..........  ..........  ---------- ---------- ---------- contig 355 short
225 .....T.IG...Y.S.-T-F--SGDVQ.A-....D...A...RSQNPVQ--------.IG.QT.---------- COLL1HUM.PRO
224 .....S.PG...Y.....-A-FRETSN.S.P-....D...A...LSSNPIQ--------.TG.ST.---------- COLL2HUM.PRO
229 ..D..K.PG.....I.-T-YTGKSHFM.P--D..VQ.....L..PGDE--------DPN..H.KT.---------- COLL3HUM.PRO
221 .MG..S.PN.V.Y.T..-G-NG..QNFK..--....K...KL..---------- ---------- ---------- MATRHUM.PRO
225 ..G..S.PK.V...T.K--YV.INTFR..--A....R....L..DPKENQRLP------NPDNSE.---------- METAHUM.PRO
225 ..F..ANTE....Y.L.H.-.T.LTRFR..--.....L..PPPDSPETP.VPTEPV.P..GT.---------- STO1HUM.PRO
224 ..F..ANTE....Y.L.N.-FTELAQFR..--.....V.....L..PPPASTEEP.VPTKSV.SGSEM.------ STO2HUM.PRO
222 ..Q.TTAAK....SAF.------TFR.....LSP..CR.V.HL..QP--WPTVTSRT---------- ---------- STO3HUM.PRO
246 ..E..S.PS.I.A.F.Q--WM.TENFV.P--D..RR....QL....ESG------FPTKM.PQ.-RT-SRPSVPDKPKNPT---------- MTM1HUM.PRO
266 ..E..SNPN.I.A.F.Q--WK.VDNFK.P--E..LR....QL..TPDGQPQPTQ.LPTVT.RR.GR.-DHRPPRPPQPPPPGGKPERPPKP MTM2HUM.PRO
254 ..E.....P..I.A.F.Q--YME-QTLQ.P--N..YR--HQR.MSPDKIPPPTR.LPTV..-PHRS...-PADPRKNDRPKPPRPPTGRPSYP MTM3HUM.PRO
171 ....VAAAHSI.R.Y.QGPVG..LR.G.PYE-.KVR-VWQL..VRESVSPTAQ.E.---------- ---------- ---------- MMP 17P
219 ..G..RYSQ....A.V.EG--YRPHFK.H--P..VA....AL..KKSPVIRDEEEE.TEL.TV.PV.TEPS---------- MMP 18P
229 ..D..K.PG.....I.-T-YTGKSHFM.P--D..VQ.....L..PGDE--------DPN..H.KT.---------- MMP 20P
157 ----------.PVDEELGFS---------- ---------- ---------- ---------- ---------- MMP 21P
218 ..M..QHGR....------H.NATLRGWKALS..ELW.LHRL..C----------LDRLFVCASWARRGF---------- MMP 22P
410 ..E..Q.PG....A.I.-T-YT--KNFR.....K....EL..ASPD--ID.GTG.TPTLG.VT.---------- GELAHUM.PRO
408 ..D..SVPE....Y.M.R--FTEGP--..H--K..V....RHL..PRPEPEPRPPTTTTPQ.TA.PTVCPTGPPTVHPSERPTAGPTGPPSA GELBHUM.PRO

277 ----------HACD--PDLTFDAITTFRREVMFFKGRHLWR-IYYDITDVE-FELIASFWPSLP---ADLQAAYENP- contig 355 long
234 ---------- ---------- ---------- ---------- ---------- ---------- ---------- contig 355 short
276 ----------K.....-SK.........I.G.......D.FYM.-TNPFYPE...-LNF.SV...Q...---NG.E.....FAD COLL1HUM.PRO
277 ----------KP....-S.........L.G.IL...D.YF...-RHPQLQR...-MNF.SL.....---TGI.....DFD COLL2HUM.PRO
282 ----------DK....--.S.SL....SL.G.T.I..D.FF...-LHPQQV.A.-LF.TK.....E...---NRID....H.S COLL3HUM.PRO
259 ---------- ---------- ---------- ---------- ---------- ---------- ---------- MATRHUM.PRO
```

Fig. 3E

```
280 ----------AL---N.S...V..VGNKIF...D.FF.L-KVSERPKTS-VN..S.L..T..---SGIE....IEA  METAHUM.PRO
288 ----------AN---A.S...VS.L.G.ILI..D..F..-KSLRKLEP.-LH..S.........---SGVD....VTS  STO1HUM.PRO
287 ----------AK---A.S....S.L.G.YL...D.YF..-RSHWNPEP.-.H..SA.....---SY.D....VNS  STO2HUM.PRO
269 -PALGPQAGIDTNEIAPLEPDAPPDA-CEAS...VS.I.G.LF...AGFV..L-RGGQLQPGYPA.ASRH.QG.---SPVD..F.DAQ  STO3HUM.PRO
314 ----------YGP-----NI---GN---.TVAML.G.MFV..E.WF..VRNNQVM.GYPMP-.GQ..RG.---.SINT....RKD  MTM1HUM.PRO
351 GPPVQPRATERPDQYGP-----NI---G---.TVAML.G.MFV....WF..VRHNRVL.NYPMP-.GH..RG.---G.IS....RQD  MTM2HUM.PRO
334 GAK----------P-----NI---GN---.NTLAIL...MFV..DQWF..VRNNRVM.GYPMQ-.TY..RG.---PSID.V....SD  MTM3HUM.PRO
225 -PPLLPEPPDNRSSAPP--RKDVPHR--CSTH...VAQI.G.AF....KYF..LTRDRHLVSLQPAQMHR..RG..LHLDSVD.V..RTS  MMP 17P
285 ----------MPDP.S--SE.D-AMMLGP.GKTYA...DYV.TVSDS---GPGPLFRVSAL.EG..GNLD--A.V.S-.R  MMP 18P
282 ----------DK---S.SL....SL.G.T.I..D.FF..-LHPQQV.A.-LF.TK.....E.---NRID....H.S  MMP 20P
167 ----------G----------RVN.L----------  MMP 21P
271 ------CDARRRLMKRLCP--SS..FCYEFP.PTVA.TPPPP---------TKTRLVPEGRNVTFRCG----------  MMP 22P
467 ----------EI.K--Q.IV..G.AQI.G.IF...D.FI..TVTPRDKPMG-PL.V.T...E.---EKID.V..A.Q  GELAHUM.PRO
492 GPTGPPTAGPSTATTVPLSPVDD..N--VNI-....AEIGNQLYL..DGKY..FSEGRGSRPQGPF...DK..A.---RK.DSVF.E.L  GELBHUM.PRO

342 RDKILVFKDENFWMIRGYAVLPDYPKSIHT-LGFPGRVKKIDAAVCDK-TTRKTYFFVGIWCWRFDEMTQTMDKGFPQRVVKHFPGISIR  contig 355 long
294 ..........-----------------------------------------------------------------------  contig 355 short
337 ..EVRF..GNKY.AVQ.QN..HG...D.YSSF...RT..H....LSEE-N.G.....ANKY..Y...YKRS..P.Y.KMIAHD....GHK  COLL1HUM.PRO
338 ..L.FL..GNQY.ALS..DI.QG...D.-SNY...SS.QA.....F---YRS.....NDQF..Y.NQR.F.EP.Y.KSISGA....ESK  COLL2HUM.PRO
343 H.L.FI.RGRK..ALN..DI.EG...K.-SE..L.KE.....S....HFE-D.G..LL.S.NQV..Y.DTNHI...DY.RLIEED....GDK  COLL3HUM.PRO
261 ----------------------------KRS-NS..K  MATRHUM.PRO
341 .NQVFL...DKY.L.SNLRPE.N.....S-F...NF.....FNP-RFYR.....DNQY..Y..RR.M..P.Y.KLIT.N.Q..GPK  METAHUM.PRO
349 K.LVFI..GNQ..A...NE.RAG..RG...-....PT.R.....IS...-EKN.....EDKY.....KRNS.EP...KQIAED....DSK  STO1HUM.PRO
348 ..TVFI..GNE..A...NE.QAG..RG...-....PTIR.....S....-EKK.....AADKY.....NS.S.EQ...RLIADD...VEPK  STO2HUM.PRO
352 GH-.WF.QGAQY.VYD.EKPVLG-.APL-.E..LVRFP--VH..LVWGPEKN.I...R.RDY...HPS.RRV.SPV.R.ATD-WR.VPSE  STO3HUM.PRO
377 GKFVF-...GDKH.VFDEASLE.G....H..-KE..RGLPTD.....LFWM-PNG.....R.NKYY..N.ELRAV.SEY.KNIKV-WE..PES  MTM1HUM.PRO
428 GRFVF-...GDRY.LF.EANLE.G..QPL-.SY.LGIPYDR..T.IWWE-P.GH.F..QEDRY...N.E..RG.P.Y.KPISV-WQ..PAS  MTM2HUM.PRO
398 GNFVF-...GNKY.VFKDTTLQ.G..HDL-IT..SGIPPHG...S.IWWE-DVG.....K.DRY..YS.EMK...P.Y.KPITV-WK..PES  MTM3HUM.PRO
```

Fig. 3F

```
310 DH..VF..GDRY.VFKDNN.EEG..RPV-SDFSL.PGG--....FSWA-HNDR....KDQLY..Y.DH.RH..P.Y.AQSPL-WR.VPST MMP 17P
356 TQW.HF..GDKV.RYINFKMS.GF..KLN------RSEPNL...LYW-PLNQ.VFL.K.SGY.QW..LAR.DFSSY.KPIKGL.T.VPNQ MMP 18P
343 H.L.FI.RGRK..ALN..DI.EG...K.-SE..L.KE....S...HFE-D.G..LL.S.NQV..Y.DTNHI...DY.RLIEED....GDK MMP 20P
174 ---------------------------------------------------------------------------------------- MMP 21P
323 -Q...HK.GKVY.-----------.KDQEPLEFSY.---------------------------------------.YLALGEA.LSI.ANA MMP 22P
529 EE.AVF.AGNEY.IYSASTLERG...PL-.S..L.PD.QRV...FNWS-KNK...I.A.DKF..YN.VKKK..P...KLIADAWNA.PDN GELAHUM.PRO
576 SK.LFF.SGRQV.VYT.AS..G--.RRLD-K..LGAD.AQVTG.LR-S-GRG.MLL.S.RRL....VKA.MV.PRSASE.DRM...VPLD GELBHUM.PRO

425 VDAAFQYK--GFF----FFSRGSTQFEYDIKTKNITRIMRTNT----WFQCKEP---------------------------------KN contig 355 long
382 ........--...----........................----.......---------------------------------.. contig 355 short
426 ...V.--MKD...----Y.FH.TR.YKF.P...R.LTLQKA.S----..N.RKN COLL1HUM.PRO
424 ...V.--QQEH..----HVFS.PRYYAF.LIAQRV..VA.G.K----.LN.RYG COLL2HUM.PRO
431 ...VY--EKN.YI----Y.FN.PI....S.WSNR.V.V.PA.S----ILW. COLL3HUM.PRO
267 MATRHUM.PRO
429 I..V.-.SKNKYY----Y.FQ..N.....FLLQR..KTLKS.S----..G. METAHUM.PRO
437 I..V.--EEF...----Y.FT..S.L.F.PNA.KV.HTLKS.S----.LN. STO1HUM.PRO
436 ...VL--QAF...----Y.FS..S...F.PNARMV.H.LKS.S----.LH. STO2HUM.PRO
436 I.....DADGY-----AY.L..RLYWKF.PVKVKALE-GFPRLVGPDF.G.A..ANTLL STO3HUM.PRO
463 PRGS.MGSDEV.----TY.YK.NKYWKFNNQKL-KVEPGYPKSALRD.MG.----------PSGGRP----DEGTEEETEVIIIEVDEEG MTM1HUM.PRO
514 PKG..LSNDAAY----TY.YK.TKYWKF.NERL-RMEPGYPKSILRDFMG.Q.HVEPGPRWPDVARPPFNPHGGAEPGADSAEGDVGDGD MTM2HUM.PRO
484 PQG..VH.EN..----TY.YKEGVL-.IQTTRYSRLEPGHPRSILKDLSG.D---GPTDRVKEGHSPP---------------DDVD--- MTM3HUM.PRO
395 L.D.MRWSDGA-----SY.F..QEYWKVLDGELEVAP-GYPQSTARD.LV.GDSQADGS---------VAAGVDAAEGPRAPPGQHDQSR MMP 17P
429 PS..MSWQDG-----RVY.FK.KVYWRLN-QQLRVEKGYPRNISHN.MH.RPRTIDTTPSGGNTTPS- --------------------- MMP 18P
431 ...VY--EKN.YI----Y.FN.PI....S.WSNR.V.V.PA.S----ILW. MMP 20P
175 ----------------------------------------------------GPGSPER S MMP 21P
363 .N------EGTYTC----------------------------VVRRQQRVLTTYSWRVRVRG MMP 22P
617 L..VVDLQGG.HS----Y.FK.AYYLKLENQSLKSVKFGSIKS--D.LG. GELAHUM.PRO
```

Fig. 3G

```
661 THDV...REKAY.CQDR.YW.V.SRS.LN----QVDQVGYVTY---DIL..P.D                         GELBHUM.PRO

471 SSFGFDINKEKAHSGGIK------------ILYHKSLSLFI----FGIVHLLKNTS----IYQ               contig 355 long
428 .................------------...........----............----...               contig 355 short
426                                                                                COLL1HUM.PRO
424                                                                                COLL2HUM.PRO
431                                                                                COLL3HUM.PRO
267                                                                                MATRHUM.PRO
429                                                                                METAHUM.PRO
437                                                                                STO1HUM.PRO
436                                                                                STO2HUM.PRO
436                                                                                STO3HUM.PRO
536 GG------------AVSAAAVVLPVL.L.LVLAVGLAVFFFRRHGTPRRLL.C.RSLLDKV                  MTM1HUM.PRO
599 GD..AGV..DGGSRVVVQMEEVARTVNVVMV.VPLL.L.CVLGLTYAL.QMQRKGAPRVLL.CKRSLQEWV      MTM2HUM.PRO
548 --------------IV..LDNTASTVKAIA.VIPCI.A.CLLVLVYTVFQFKRKGTPRHIL.CKRSMQEWV      MTM3HUM.PRO
470 .ED.YEVCSCTS--------GASSPPGAPGP.VAATML.LLPPL-----------.PGALWTAAQALT--L      MMP 17P
488 ------------GT..TLDTTLSATETT--------------FEY                                MMP 18P
175                                                                                MMP 20P
363                                                                                MMP 21P
617                                                                                MMP 22P
661                                                                                GELAHUM.PRO
                                                                                   GELBHUM.PRO
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Fig. 3H

SEQUENCE LISTING

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Wang, Kai
Smith, Ryan
Fajardo, Mark
Moss, Patrick

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tat gga ggt ctg cct aag gaa cct gct aag cca aag gaa ccc act ata       96
Tyr Gly Gly Leu Pro Lys Glu Pro Ala Lys Pro Lys Glu Pro Thr Ile
            20                  25                  30

ccc cat gcc tgt gac cct gac ttg act ttt gac gct atc aca act ttc      144
Pro His Ala Cys Asp Pro Asp Leu Thr Phe Asp Ala Ile Thr Thr Phe
        35                  40                  45

cgc aga gaa gta atg ttc ttt aaa ggc agg cac cta tgg agg atc tat      192
Arg Arg Glu Val Met Phe Phe Lys Gly Arg His Leu Trp Arg Ile Tyr
    50                  55                  60

tat gat atc acg gat gtt gag ttt gaa tta att gct tca ttc tgg cca      240
Tyr Asp Ile Thr Asp Val Glu Phe Glu Leu Ile Ala Ser Phe Trp Pro
65                  70                  75                  80

tct ctg cca gct gat ctg caa gct gca tac gag aac ccc aga gat aag      288
Ser Leu Pro Ala Asp Leu Gln Ala Ala Tyr Glu Asn Pro Arg Asp Lys
                85                  90                  95

att ctg gtt ttt aaa gat gaa aac ttc tgg atg atc aga gga tat gct      336
Ile Leu Val Phe Lys Asp Glu Asn Phe Trp Met Ile Arg Gly Tyr Ala
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            100                 105                 110

gtc ttg cca gat tat ccc aaa tcc atc cat aca tta ggt ttt cca gga      384
Val Leu Pro Asp Tyr Pro Lys Ser Ile His Thr Leu Gly Phe Pro Gly
        115                 120                 125

cgt gtg aag aaa ata gat gca gcc gtc tgt gat aag acc aca aga aaa      432
Arg Val Lys Lys Ile Asp Ala Ala Val Cys Asp Lys Thr Thr Arg Lys
    130                 135                 140

acc tac ttc ttt gtg ggc att tgg tgc tgg agg ttt gat gaa atg acc      480
Thr Tyr Phe Phe Val Gly Ile Trp Cys Trp Arg Phe Asp Glu Met Thr
145                 150                 155                 160

caa acc atg gac aaa ggg ttc ccg cag aga gtg gta aaa cac ttt cct      528
Gln Thr Met Asp Lys Gly Phe Pro Gln Arg Val Val Lys His Phe Pro
                165                 170                 175

gga atc agt atc cgt gtt gat gct gct ttc cag tac aaa gga ttc ttc      576
Gly Ile Ser Ile Arg Val Asp Ala Ala Phe Gln Tyr Lys Gly Phe Phe
            180                 185                 190

ttt ttc agc cgt gga tca acg caa ttt gaa tac gac att aag aca aag      624
Phe Phe Ser Arg Gly Ser Thr Gln Phe Glu Tyr Asp Ile Lys Thr Lys
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aat att acc cga atc atg aga act aat act tgg ttt caa tgc aaa gaa      672
Asn Ile Thr Arg Ile Met Arg Thr Asn Thr Trp Phe Gln Cys Lys Glu
    210                 215                 220

cca aag aac tcc tca ttt ggt ttt gat atc aac aag gaa aaa gca cat      720
Pro Lys Asn Ser Ser Phe Gly Phe Asp Ile Asn Lys Glu Lys Ala His
225                 230                 235                 240

tca gga ggc ata aag ata ttg tat cat aag agt tta agc ttg ttt att      768
Ser Gly Gly Ile Lys Ile Leu Tyr His Lys Ser Leu Ser Leu Phe Ile
                245                 250                 255

ttt ggt att gtt cat ttg ctg aaa aac act tct att tat caa              810
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His Ala Cys Asp Pro Asp Leu Thr Phe Asp Ala Ile Thr Thr Phe Arg
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Arg Glu Val Met Phe Phe Lys Gly Arg His Leu Trp Arg Ile Tyr Tyr
    50                  55                  60
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Asp Ile Thr Asp Val Glu Phe Glu Leu Ile Ala Ser Phe Trp Pro Ser
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Leu Val Phe Lys Asp Glu Asn Phe Trp Met Ile Arg Gly Tyr Ala Val
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Leu Pro Asp Tyr Pro Lys Ser Ile His Thr Leu Gly Phe Pro Gly Arg
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Val Lys Lys Ile Asp Ala Ala Val Cys Asp Lys Thr Thr Arg Lys Thr
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Tyr Phe Phe Val Gly Ile Trp Cys Trp Arg Phe Asp Glu Met Thr Gln
145                 150                 155                 160
Thr Met Asp Lys Gly Phe Pro Gln Arg Val Val Lys His Phe Pro Gly
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Ile Ser Ile Arg Val Asp Ala Ala Phe Gln Tyr Lys Gly Phe Phe Phe
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Lys Asn Ser Ser Phe Gly Phe Asp Ile Asn Lys Glu Lys Ala His Ser
225                 230                 235                 240
Gly Gly Ile Lys Ile Leu Tyr His Lys Ser Leu Ser Leu Phe Ile Phe
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165 170 175
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Lys Pro Lys Glu Pro Thr Ile Pro His Ala Cys Asp Pro Asp Leu Thr
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245 250 255
Arg His Leu Trp Arg Ile Tyr Tyr Asp Ile Thr Asp Val Glu Phe Glu
260 265 270
Leu Ile Ala Ser Phe Trp Pro Ser Leu Pro Asp Leu Gln Ala Ala Tyr
275 280 285
Glu Asn Pro Arg Asp Lys Ile Leu Val Phe Lys Asp Glu Asn Phe Trp
290 295 300
Met Ile Arg Gly Tyr Ala Val Leu Pro Asp Tyr Pro Lys Ser Ile His
305 310 315 320
Thr Leu Gly Phe Pro Gly Arg Val Lys Lys Ile Asp Ala Ala Val Cys
325 330 335
Asp Lys Thr Thr Arg Lys Thr Tyr Phe Phe Val Gly Ile Trp Cys Trp
340 345 350
Arg Phe Asp Glu Met Thr Gln Thr Met Asp Lys Gly Phe Pro Gln Arg
355 360 365
Val Val Lys His Phe Pro Gly Ile Ser Ile Arg Val Asp Ala Ala Phe
370 375 380
Gln Tyr Lys Gly Phe Phe Phe Phe Arg Gly Ser Thr Gln Phe Glu Tyr
385 390 395 400
Asp Ile Lys Thr Lys Asn Ile Thr Arg Ile Met Arg Thr Asn Thr Trp

```
                405                 410                 415
Phe Gln Cys Lys Glu Pro Lys Asn Ser Ser Phe Gly Phe Asp Ile Asn
            420                 425                 430
Lys Glu Lys Ala His Ser Gly Gly Ile Lys Ile Leu Tyr His Lys Ser
        435                 440                 445
Ser Leu Phe Ile Phe Gly Ile Val His Leu Leu Lys Asn Thr Ser Ile
    450                 455                 460
Tyr Gln
465
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<210> 5
<211> 1841
<212> DNA
<213> Homo sapien

<400> 5

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gaaagagagg aatgaagcgc cttctgcttc tgtttttgtt ctttataaca ttttcttctg     60
catttccctt agtccggatg atggaaaatg aagaaaatgt gcaactggct caggcatatc    120
tcaaccagtt ctactctctt gaaatagaag ggaatcatct tgttcaaagc aagaatagga    180
gtctcataga tgacaaaatt cgggaaatgc aagcattttt tggattgaca gtgactggaa    240
gactggactc aaacaccctt gagatcatga agacacccag gtgtggggtg cctgatgtgg    300
gccagtatgg ctacaccctc cctgggtgga gaaaatacaa cctcacctac agaataataa    360
actatactcc ggatatggca cgagctgctg tggatgaggc tatccaagaa ggtttagaag    420
tgtggagcaa agtcactcca ctaaaattca ccaagatttc aaaggggatt gcagacatca    480
tgattgcctt taggactcga gtccatggtc ggtgtcctcg ctattttgat ggtcccttgg    540
gagttcttgg ccatgccttt cctcctggtc cgggtctggg tggtgacact cattttgatg    600
aggatgaaaa ctggaccaag gatggagcag gattcaactt gtttcttgtg gctgctcatg    660
aatttggtca tgcactgggg ctctctcact ccaatgatca aacagccttg atgttcccaa    720
attatgtctc cctggatccc agaaaatacc cactttctca ggatgatatc aatggaatcc    780
agtccatcta tggaggtctg cctaaggaac ctgctaagcc aaaggaaccc actataccc     840
atgcctgtga ccctgacttg acttttgacg ctatcacaac tttccgcaga gaagtaatgt    900
tctttaaagg caggcaccta tggaggatct attatgatat cacggatgtt gagtttgaat    960
taattgcttc attctggcca tctctgccag ctgatctgca agctgcatac gagaacccca   1020
gagataagat tctggttttt aaagatgaaa acttctggat gatcagagga tatgctgtct   1080
tgccagatta tcccaaatcc atccatacat taggttttcc aggacgtgtg aagaaaatag   1140
atgcagccgt ctgtgataag accacaagaa aaacctactt ctttgtgggc atttggtgct   1200
ggaggtttga tgaaatgacc caaaccatgg acaaagggtt cccgcagaga gtggtaaaac   1260
actttcctgg aatcagtatc cgtgttgatg ctgctttcca gtacaaagga ttcttctttt   1320
tcagccgtgg atcaacgcaa tttgaatacg acattaagac aaagaatatt acccgaatca   1380
tgagaactaa tacttggttt caatgcaaag aaccaaagaa ctcctcattt ggttttgata   1440
tcaacaagga aaaagcacat tcaggaggca taaagatatt gtatcataag agtttaagct   1500
tgtttatttt tggtattgtt catttgctga aaaacacttc tatttatcaa taaattcata   1560
gacctaaaat aaacctcaac aggtctttta atataaattc tgcttcaaaa tagaataaaa   1620
ccattcttta acaacaagtt gctggtccta gttctaaata tccaaattca atggccattt   1680
tgagctgcct gattctttta ataggaagtt attatgtaga aacaaaaatc tctgactgta   1740
ctttaagcct atttcatgct ttgtggactt ggagaagaca tgtcttataa ctgaatactg   1800
aaacatttat taaaccaatc tttagcattc tgaaaaaaaa a                       1841
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<210> 6
<211> 513
<212> PRT
<213> Homo sapien

<400> 6

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Met Lys Arg Leu Leu Leu Leu Phe Leu Phe Phe Ile Thr Phe Ser Ser
 1               5                  10                  15
Ala Phe Pro Leu Val Arg Met Met Glu Asn Glu Glu Asn Val Gln Leu
            20                  25                  30
```

```
Ala Gln Ala Tyr Leu Asn Gln Phe Tyr Ser Leu Glu Ile Glu Gly Asn
        35                  40                  45
His Leu Val Gln Ser Lys Asn Arg Ser Leu Ile Asp Asp Lys Ile Arg
    50                  55                  60
Glu Met Gln Ala Phe Phe Gly Leu Thr Val Thr Gly Arg Leu Asp Ser
65                  70                  75                  80
Asn Thr Leu Glu Ile Met Lys Thr Pro Arg Cys Gly Val Pro Asp Val
                85                  90                  95
Gly Gln Tyr Gly Tyr Thr Leu Pro Gly Trp Arg Lys Tyr Asn Leu Thr
            100                 105                 110
Tyr Arg Ile Ile Asn Tyr Thr Pro Asp Met Ala Arg Ala Ala Val Asp
        115                 120                 125
Glu Ala Ile Gln Glu Gly Leu Glu Val Trp Ser Lys Val Thr Pro Leu
    130                 135                 140
Lys Phe Thr Lys Ile Ser Lys Gly Ile Ala Asp Ile Met Ile Ala Phe
145                 150                 155                 160
Arg Thr Arg Val His Gly Arg Cys Pro Arg Tyr Phe Asp Gly Pro Leu
                165                 170                 175
Gly Val Leu Gly His Ala Phe Pro Pro Gly Pro Gly Leu Gly Gly Asp
            180                 185                 190
Thr His Phe Asp Glu Asp Glu Asn Trp Thr Lys Asp Gly Ala Gly Phe
        195                 200                 205
Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ala Leu Gly Leu
    210                 215                 220
Ser His Ser Asn Asp Gln Thr Ala Leu Met Phe Pro Asn Tyr Val Ser
225                 230                 235                 240
Leu Asp Pro Arg Lys Tyr Pro Leu Ser Gln Asp Asp Ile Asn Gly Ile
                245                 250                 255
Gln Ser Ile Tyr Gly Gly Leu Pro Lys Glu Pro Ala Lys Pro Lys Glu
            260                 265                 270
Pro Thr Ile Pro His Ala Cys Asp Pro Asp Leu Thr Phe Asp Ala Ile
        275                 280                 285
Thr Thr Phe Arg Arg Glu Val Met Phe Phe Lys Gly Arg His Leu Trp
    290                 295                 300
Arg Ile Tyr Tyr Asp Ile Thr Asp Val Glu Phe Glu Leu Ile Ala Ser
305                 310                 315                 320
Phe Trp Pro Ser Leu Pro Ala Asp Leu Gln Ala Ala Tyr Glu Asn Pro
                325                 330                 335
Arg Asp Lys Ile Leu Val Phe Lys Asp Glu Asn Phe Trp Met Ile Arg
            340                 345                 350
Gly Tyr Ala Val Leu Pro Asp Tyr Pro Lys Ser Ile His Thr Leu Gly
        355                 360                 365
Phe Pro Gly Arg Val Lys Lys Ile Asp Ala Ala Val Cys Asp Lys Thr
    370                 375                 380
Thr Arg Lys Thr Tyr Phe Phe Val Gly Ile Trp Cys Trp Arg Phe Asp
385                 390                 395                 400
Glu Met Thr Gln Thr Met Asp Lys Gly Phe Pro Gln Arg Val Val Lys
                405                 410                 415
His Phe Pro Gly Ile Ser Ile Arg Val Asp Ala Ala Phe Gln Tyr Lys
            420                 425                 430
Gly Phe Phe Phe Phe Ser Arg Gly Ser Thr Gln Phe Glu Tyr Asp Ile
        435                 440                 445
Lys Thr Lys Asn Ile Thr Arg Ile Met Arg Thr Asn Thr Trp Phe Gln
    450                 455                 460
Cys Lys Glu Pro Lys Asn Ser Ser Phe Gly Phe Asp Ile Asn Lys Glu
465                 470                 475                 480
Lys Ala His Ser Gly Gly Ile Lys Ile Leu Tyr His Lys Ser Leu Ser
                485                 490                 495
```

Leu Phe Ile Phe Gly Ile Val His Leu Leu Lys Asn Thr Ser Ile Tyr
500 505 510
Gln

<210> 7
<211> 27
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(27)
<223> Xaa = any amino acid

<400> 7
Leu Val Ala Ala His Glu Leu Gly His Xaa Leu Gly Leu Xaa His Ser
1 5 10 15
Xaa Xaa Xaa Xaa Ala Xaa Met Ser Ser Ser Tyr
20 25

<210> 8
<211> 37
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (1)...(37)
<223> Xaa = any amino acid

<400> 8
His Gly Asp Xaa Xaa Pro Phe Asp Gly Xaa Xaa Xaa Xaa Leu Ala His
1 5 10 15
Ala Phe Xaa Pro Gly Xaa Gly Xaa Gly Gly Asp Xaa His Pro Asp Xaa
20 25 30
Asp Glu Xaa Trp Thr
35

<210> 9
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 9
tgatatcata atagatcctc cataggtgcc 30

<210> 10
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 10
ttccttaggc agacctccat agatggactg g 31

<210> 11
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 11
cctaaggaac ctgctaagcc aaaggaa 27

<210> 12
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 12
ccgcagagaa gtaatgttct ttaaa 25

<210> 13
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 13
ccgcagagaa gtaatgttct ttaaa 25

<210> 14
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 14
tgatatcata atagatcctc cataggtgcc 30

<210> 15
<211> 411
<212> DNA
<213> Homo sapien

<400> 15
agaaaatacc cactttctca ggatgatatc aatggaatcc agtccatcta tggaggtctg 60
cctaaggaac ctgctaagcc aaaggaaccc actatacccc atgcctgtga ccctgacttg 120
acttttgacg ctatcacaac tttccgcaga gaagtaatgt tctttaaagg caggcaccta 180
tggaggatct attatgatat cacggatgtt gagtttgaat taattgcttc attctggcca 240
tctctgccag ctgatctgca agctgcatac gagaacccca gagataagat tctggttttt 300

aaagatgaaa acttctggat gatcagagga tatgctgtct tgccagatta tcccaaatcc 360
atccatacat taggttttcc aggacgtgtg aagaaaatag atgcagccgt c 411

<210> 16
<211> 382
<212> DNA
<213> Homo sapiens

<400> 16
ttttttttt tattttaggt ctatgaattt attgataaat agaagtgttt ttcagcaaat 60
gaacaatacc aaaaataaac aagcttaaac tcttatgata caatatcttt atgcctcctg 120
aatgtgcttt ttccttgttg atatcaaaac caaatgagga gttctttggt tctttgcatt 180
gaaaccaagt attagttctc atgattcggg taatattctt tgtcttaatg tcgtattcaa 240
attgcgttga tccacggctg aaaaagaaga atcctttgta ctggaaagca gcatcaacac 300
ggatactgat tccaggaaag tgttttacca ctctctgcgg gaaccctttg tccatggttt 360
gggtcatttc atcaaacctc ca 382

<210> 17
<211> 12
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (3)...(3)
<223> Xaa = any amino acid

<221> VARIANT
<222> (6)...(7)
<223> Xaa = any amino acid

<221> VARIANT
<222> (9)...(10)
<223> Xaa = any amino acid

<221> VARIANT
<222> (12)...(12)
<223> Xaa = Serine or Threonine

<400> 17
His Glu Xaa Phe His Xaa Xaa Gly Xaa Xaa His Xaa
1 5 10

<210> 18
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (5)...(5)
<223> Xaa = any amino acid

<400> 18
Pro Arg Cys Gly Xaa Pro Asp
1 5

<210> 19

<211> 469
<212> PRT
<213> Homo sapiens

<400> 19

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Met His Ser Phe Pro Pro Leu Leu Leu Leu Leu Phe Trp Gly Val Val
 1               5                  10                  15
Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp
            20                  25                  30
Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly
        35                  40                  45
Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu
    50                  55                  60
Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp
65                  70                  75                  80
Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp
                85                  90                  95
Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr
            100                 105                 110
His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala
        115                 120                 125
Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val
    130                 135                 140
Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met
145                 150                 155                 160
Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly
                165                 170                 175
Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly
            180                 185                 190
Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg
        195                 200                 205
Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu
    210                 215                 220
Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr
225                 230                 235                 240
Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile
                245                 250                 255
Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro
            260                 265                 270
Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr
        275                 280                 285
Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg
    290                 295                 300
Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe
305                 310                 315                 320
Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp
                325                 330                 335
Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln
            340                 345                 350
Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe
        355                 360                 365
Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu
    370                 375                 380
Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr
385                 390                 395                 400
Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala
                405                 410                 415
His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys
```

```
            420                 425                 430
Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp
        435                 440                 445
Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe
    450                 455                 460
Asn Cys Arg Lys Asn
465
```

<210> 20
<211> 467
<212> PRT
<213> Homo sapiens

<400> 20

```
Met Phe Ser Leu Lys Thr Leu Pro Phe Leu Leu Leu Leu His Val Gln
 1               5                  10                  15
Ile Ser Lys Ala Phe Pro Val Ser Ser Lys Glu Lys Asn Thr Lys Thr
            20                  25                  30
Val Gln Asp Tyr Leu Glu Lys Phe Tyr Gln Leu Pro Ser Asn Gln Tyr
        35                  40                  45
Gln Ser Thr Arg Lys Asn Gly Thr Asn Val Ile Val Glu Lys Leu Lys
    50                  55                  60
Glu Met Gln Arg Phe Phe Gly Leu Asn Val Thr Gly Lys Pro Asn Glu
65                  70                  75                  80
Glu Thr Leu Asp Met Met Lys Lys Pro Arg Cys Gly Val Pro Asp Ser
                85                  90                  95
Gly Gly Phe Met Leu Thr Pro Gly Asn Pro Lys Trp Glu Arg Thr Asn
            100                 105                 110
Leu Thr Tyr Arg Ile Arg Asn Tyr Thr Pro Gln Leu Ser Glu Ala Glu
        115                 120                 125
Val Glu Arg Ala Ile Lys Asp Ala Phe Glu Leu Trp Ser Val Ala Ser
    130                 135                 140
Pro Leu Ile Phe Thr Arg Ile Ser Gln Gly Glu Ala Asp Ile Asn Ile
145                 150                 155                 160
Ala Phe Tyr Gln Arg Asp His Gly Asp Asn Ser Pro Phe Asp Gly Pro
                165                 170                 175
Asn Gly Ile Leu Ala His Ala Phe Gln Pro Gly Gln Gly Ile Gly Gly
            180                 185                 190
Asp Ala His Phe Asp Ala Glu Glu Thr Trp Thr Asn Thr Ser Ala Asn
        195                 200                 205
Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ser Leu Gly
    210                 215                 220
Leu Ala His Ser Ser Asp Pro Gly Ala Leu Met Tyr Pro Asn Tyr Ala
225                 230                 235                 240
Phe Arg Glu Thr Ser Asn Tyr Ser Leu Pro Gln Asp Asp Ile Asp Gly
                245                 250                 255
Ile Gln Ala Ile Tyr Gly Leu Ser Ser Asn Pro Ile Gln Pro Thr Gly
            260                 265                 270
Pro Ser Thr Pro Lys Pro Cys Asp Pro Ser Leu Thr Phe Asp Ala Ile
        275                 280                 285
Thr Thr Leu Arg Gly Glu Ile Leu Phe Phe Lys Asp Arg Tyr Phe Trp
    290                 295                 300
Arg Arg His Pro Gln Leu Gln Arg Val Glu Met Asn Phe Ile Ser Leu
305                 310                 315                 320
Phe Trp Pro Ser Leu Pro Thr Gly Ile Gln Ala Ala Tyr Glu Asp Phe
                325                 330                 335
Asp Arg Asp Leu Ile Phe Leu Phe Lys Gly Asn Gln Tyr Trp Ala Leu
            340                 345                 350
```

```
Ser Gly Tyr Asp Ile Leu Gln Gly Tyr Pro Lys Asp Ile Ser Asn Tyr
        355                 360                 365
Gly Phe Pro Ser Ser Val Gln Ala Ile Asp Ala Ala Val Phe Tyr Arg
    370                 375                 380
Ser Lys Thr Tyr Phe Phe Val Asn Asp Gln Phe Trp Arg Tyr Asp Asn
385                 390                 395                 400
Gln Arg Gln Phe Met Glu Pro Gly Tyr Pro Lys Ser Ile Ser Gly Ala
                405                 410                 415
Phe Pro Gly Ile Glu Ser Lys Val Asp Ala Val Phe Gln Gln Glu His
            420                 425                 430
Phe Phe His Val Phe Ser Gly Pro Arg Tyr Tyr Ala Phe Asp Leu Ile
        435                 440                 445
Ala Gln Arg Val Thr Arg Val Ala Arg Gly Asn Lys Trp Leu Asn Cys
    450                 455                 460
Arg Tyr Gly
465

<210> 21
<211> 471
<212> PRT
<213> Homo sapiens

<400> 21
Met His Pro Gly Val Leu Ala Ala Phe Leu Phe Leu Ser Trp Thr His
 1               5                  10                  15
Cys Arg Ala Leu Pro Leu Pro Ser Gly Gly Asp Glu Asp Asp Leu Ser
            20                  25                  30
Glu Glu Asp Leu Gln Phe Ala Glu Arg Tyr Leu Arg Ser Tyr Tyr His
        35                  40                  45
Pro Thr Asn Leu Ala Gly Ile Leu Lys Glu Asn Ala Ala Ser Ser Met
    50                  55                  60
Thr Glu Arg Leu Arg Glu Met Gln Ser Phe Phe Gly Leu Glu Val Thr
65                  70                  75                  80
Gly Lys Leu Asp Asp Asn Thr Leu Asp Val Met Lys Lys Pro Arg Cys
                85                  90                  95
Gly Val Pro Asp Val Gly Glu Tyr Asn Val Phe Pro Arg Thr Leu Lys
            100                 105                 110
Trp Ser Lys Met Asn Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp
        115                 120                 125
Met Thr His Ser Glu Val Glu Lys Ala Phe Lys Lys Ala Phe Lys Val
    130                 135                 140
Trp Ser Asp Val Thr Pro Leu Asn Phe Thr Arg Leu His Asp Gly Ile
145                 150                 155                 160
Ala Asp Ile Met Ile Ser Phe Gly Ile Lys Glu His Gly Asp Phe Tyr
                165                 170                 175
Pro Phe Asp Gly Pro Ser Gly Leu Leu Ala His Ala Phe Pro Pro Gly
            180                 185                 190
Pro Asn Tyr Gly Gly Asp Ala His Phe Asp Asp Asp Glu Thr Trp Thr
        195                 200                 205
Ser Ser Ser Lys Gly Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe
    210                 215                 220
Gly His Ser Leu Gly Leu Asp His Ser Lys Asp Pro Gly Ala Leu Met
225                 230                 235                 240
Phe Pro Ile Tyr Thr Tyr Thr Gly Lys Ser His Phe Met Leu Pro Asp
                245                 250                 255
Asp Asp Val Gln Gly Ile Gln Ser Leu Tyr Gly Pro Gly Asp Glu Asp
            260                 265                 270
Pro Asn Pro Lys His Pro Lys Thr Pro Asp Lys Cys Asp Pro Ser Leu
```

```
        275                 280                 285
Ser Leu Asp Ala Ile Thr Ser Leu Arg Gly Glu Thr Met Ile Phe Lys
    290                 295                 300
Asp Arg Phe Phe Trp Arg Leu His Pro Gln Gln Val Asp Ala Glu Leu
305                 310                 315                 320
Phe Leu Thr Lys Ser Phe Trp Pro Glu Leu Pro Asn Arg Ile Asp Ala
                325                 330                 335
Ala Tyr Glu His Pro Ser His Asp Leu Ile Phe Ile Phe Arg Gly Arg
            340                 345                 350
Lys Phe Trp Ala Leu Asn Gly Tyr Asp Ile Leu Glu Gly Tyr Pro Lys
        355                 360                 365
Lys Ile Ser Glu Leu Gly Leu Pro Lys Glu Val Lys Lys Ile Ser Ala
    370                 375                 380
Ala Val His Phe Glu Asp Thr Gly Lys Thr Leu Leu Phe Ser Gly Asn
385                 390                 395                 400
Gln Val Trp Arg Tyr Asp Asp Thr Asn His Ile Met Asp Lys Asp Tyr
                405                 410                 415
Pro Arg Leu Ile Glu Glu Asp Phe Pro Gly Ile Gly Asp Lys Val Asp
            420                 425                 430
Ala Val Tyr Glu Lys Asn Gly Tyr Ile Tyr Phe Phe Asn Gly Pro Ile
        435                 440                 445
Gln Phe Glu Tyr Ser Ile Trp Ser Asn Arg Ile Val Arg Val Met Pro
    450                 455                 460
Ala Asn Ser Ile Leu Trp Cys
465                 470

<210> 22
<211> 267
<212> PRT
<213> Homo sapiens

<400> 22
Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu
 1               5                  10                  15
Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp
            20                  25                  30
Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
        35                  40                  45
Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
    50                  55                  60
Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
65                  70                  75                  80
Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
                85                  90                  95
Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
            100                 105                 110
Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
        115                 120                 125
Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
    130                 135                 140
Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
145                 150                 155                 160
Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
                165                 170                 175
Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
            180                 185                 190
Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
        195                 200                 205
```

```
Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
    210                 215                 220
Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
225                 230                 235                 240
Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
                245                 250                 255
Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
            260                 265
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<210> 23
<211> 470
<212> PRT
<213> Homo sapiens

<400> 23

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Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala
 1               5                  10                  15
Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe
            20                  25                  30
Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu
        35                  40                  45
Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile
    50                  55                  60
Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp
65                  70                  75                  80
Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp
                85                  90                  95
Val His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His
            100                 105                 110
Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu
        115                 120                 125
Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val
    130                 135                 140
Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu
145                 150                 155                 160
Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly
                165                 170                 175
Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly
            180                 185                 190
Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly
        195                 200                 205
Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu
    210                 215                 220
Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr
225                 230                 235                 240
Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg
                245                 250                 255
Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro
            260                 265                 270
Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe
        275                 280                 285
Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg
    290                 295                 300
Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu
305                 310                 315                 320
Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr
                325                 330                 335
Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr
```

```
            340                 345                 350
Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile
        355                 360                 365
His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val
    370                 375                 380
Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr
385                 390                 395                 400
Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys
                405                 410                 415
Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val
            420                 425                 430
Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln
        435                 440                 445
Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser
    450                 455                 460
Asn Ser Trp Phe Gly Cys
465                 470

<210> 24
<211> 477
<212> PRT
<213> Homo sapiens

<400> 24
Met Lys Ser Leu Pro Ile Leu Leu Leu Leu Cys Val Ala Val Cys Ser
 1               5                  10                  15
Ala Tyr Pro Leu Asp Gly Ala Ala Arg Gly Glu Asp Thr Ser Met Asn
            20                  25                  30
Leu Val Gln Lys Tyr Leu Glu Asn Tyr Tyr Asp Leu Lys Lys Asp Val
        35                  40                  45
Lys Gln Phe Val Arg Arg Lys Asp Ser Gly Pro Val Val Lys Lys Ile
    50                  55                  60
Arg Glu Met Gln Lys Phe Leu Gly Leu Glu Val Thr Gly Lys Leu Asp
65                  70                  75                  80
Ser Asp Thr Leu Glu Val Met Arg Lys Pro Arg Cys Gly Val Pro Asp
                85                  90                  95
Val Gly His Phe Arg Thr Phe Pro Gly Ile Pro Lys Trp Arg Lys Thr
            100                 105                 110
His Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Lys Asp
        115                 120                 125
Ala Val Asp Ser Ala Val Glu Lys Ala Leu Lys Val Trp Glu Glu Val
    130                 135                 140
Thr Pro Leu Thr Phe Ser Arg Leu Tyr Glu Gly Glu Ala Asp Ile Met
145                 150                 155                 160
Ile Ser Phe Ala Val Arg Glu His Gly Asp Phe Tyr Pro Phe Asp Gly
                165                 170                 175
Pro Gly Asn Val Leu Ala His Ala Tyr Ala Pro Gly Pro Gly Ile Asn
            180                 185                 190
Gly Asp Ala His Phe Asp Asp Asp Glu Gln Trp Thr Lys Asp Thr Thr
        195                 200                 205
Gly Thr Asn Leu Phe Leu Val Ala Ala His Glu Ile Gly His Ser Leu
    210                 215                 220
Gly Leu Phe His Ser Ala Asn Thr Glu Ala Leu Met Tyr Pro Leu Tyr
225                 230                 235                 240
His Ser Leu Thr Asp Leu Thr Arg Phe Arg Leu Ser Gln Asp Asp Ile
                245                 250                 255
Asn Gly Ile Gln Ser Leu Tyr Gly Pro Pro Pro Asp Ser Pro Glu Thr
            260                 265                 270
```

```
Pro Leu Val Pro Thr Glu Pro Val Pro Pro Glu Pro Gly Thr Pro Ala
        275                 280                 285
Asn Cys Asp Pro Ala Leu Ser Phe Asp Ala Val Ser Thr Leu Arg Gly
    290                 295                 300
Glu Ile Leu Ile Phe Lys Asp Arg His Phe Trp Arg Lys Ser Leu Arg
305                 310                 315                 320
Lys Leu Glu Pro Glu Leu His Leu Ile Ser Ser Phe Trp Pro Ser Leu
                325                 330                 335
Pro Ser Gly Val Asp Ala Ala Tyr Glu Val Thr Ser Lys Asp Leu Val
            340                 345                 350
Phe Ile Phe Lys Gly Asn Gln Phe Trp Ala Ile Arg Gly Asn Glu Val
        355                 360                 365
Arg Ala Gly Tyr Pro Arg Gly Ile His Thr Leu Gly Phe Pro Pro Thr
    370                 375                 380
Val Arg Lys Ile Asp Ala Ala Ile Ser Asp Lys Glu Lys Asn Lys Thr
385                 390                 395                 400
Tyr Phe Phe Val Glu Asp Lys Tyr Trp Arg Phe Asp Glu Lys Arg Asn
                405                 410                 415
Ser Met Glu Pro Gly Phe Pro Lys Gln Ile Ala Glu Asp Phe Pro Gly
            420                 425                 430
Ile Asp Ser Lys Ile Asp Ala Val Phe Glu Glu Phe Gly Phe Phe Tyr
        435                 440                 445
Phe Phe Thr Gly Ser Ser Gln Leu Glu Phe Asp Pro Asn Ala Lys Lys
    450                 455                 460
Val Thr His Thr Leu Lys Ser Asn Ser Trp Leu Asn Cys
465                 470                 475

<210> 25
<211> 476
<212> PRT
<213> Homo sapiens

<400> 25
Met Met His Leu Ala Phe Leu Val Leu Leu Cys Leu Pro Val Cys Ser
 1               5                  10                  15
Ala Tyr Pro Leu Ser Gly Ala Ala Lys Glu Glu Asp Ser Asn Lys Asp
            20                  25                  30
Leu Ala Gln Gln Tyr Leu Glu Lys Tyr Tyr Asn Leu Glu Lys Asp Val
        35                  40                  45
Lys Gln Phe Arg Arg Lys Asp Ser Asn Leu Ile Val Lys Lys Ile Gln
    50                  55                  60
Gly Met Gln Lys Phe Leu Gly Leu Glu Val Thr Gly Lys Leu Asp Thr
65                  70                  75                  80
Asp Thr Leu Glu Val Met Arg Lys Pro Arg Cys Gly Val Pro Asp Val
                85                  90                  95
Gly His Phe Ser Ser Phe Pro Gly Met Pro Lys Trp Arg Lys Thr His
            100                 105                 110
Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Arg Asp Ala
        115                 120                 125
Val Asp Ser Ala Ile Glu Lys Ala Leu Lys Val Trp Glu Glu Val Thr
    130                 135                 140
Pro Leu Thr Phe Ser Arg Leu Tyr Glu Gly Glu Ala Asp Ile Met Ile
145                 150                 155                 160
Ser Phe Ala Val Lys Glu His Gly Asp Phe Tyr Ser Phe Asp Gly Pro
                165                 170                 175
Gly His Ser Leu Ala His Ala Tyr Pro Pro Gly Pro Gly Leu Tyr Gly
            180                 185                 190
Asp Ile His Phe Asp Asp Asp Glu Lys Trp Thr Glu Asp Ala Ser Gly
```

```
        195                 200                 205
Thr Asn Leu Phe Leu Val Ala Ala His Glu Leu Gly His Ser Leu Gly
    210                 215                 220
Leu Phe His Ser Ala Asn Thr Glu Ala Leu Met Tyr Pro Leu Tyr Asn
225                 230                 235                 240
Ser Phe Thr Glu Leu Ala Gln Phe Arg Leu Ser Gln Asp Asp Val Asn
                245                 250                 255
Gly Ile Gln Ser Leu Tyr Gly Pro Pro Pro Ala Ser Thr Glu Glu Pro
            260                 265                 270
Leu Val Pro Thr Lys Ser Val Pro Ser Gly Ser Glu Met Pro Ala Lys
        275                 280                 285
Cys Asp Pro Ala Leu Ser Phe Asp Ala Ile Ser Thr Leu Arg Gly Glu
    290                 295                 300
Tyr Leu Phe Phe Lys Asp Arg Tyr Phe Trp Arg Arg Ser His Trp Asn
305                 310                 315                 320
Pro Glu Pro Glu Phe His Leu Ile Ser Ala Phe Trp Pro Ser Leu Pro
                325                 330                 335
Ser Tyr Leu Asp Ala Ala Tyr Glu Val Asn Ser Arg Asp Thr Val Phe
            340                 345                 350
Ile Phe Lys Gly Asn Glu Phe Trp Ala Ile Arg Gly Asn Glu Val Gln
        355                 360                 365
Ala Gly Tyr Pro Arg Gly Ile His Thr Leu Gly Phe Pro Pro Thr Ile
    370                 375                 380
Arg Lys Ile Asp Ala Ala Val Ser Asp Lys Glu Lys Lys Lys Thr Tyr
385                 390                 395                 400
Phe Phe Ala Ala Asp Lys Tyr Trp Arg Phe Asp Glu Asn Ser Gln Ser
                405                 410                 415
Met Glu Gln Gly Phe Pro Arg Leu Ile Ala Asp Asp Phe Pro Gly Val
            420                 425                 430
Glu Pro Lys Val Asp Ala Val Leu Gln Ala Phe Gly Phe Phe Tyr Phe
        435                 440                 445
Phe Ser Gly Ser Ser Gln Phe Glu Phe Asp Pro Asn Ala Arg Met Val
    450                 455                 460
Thr His Ile Leu Lys Ser Asn Ser Trp Leu His Cys
465                 470                 475

<210> 26
<211> 488
<212> PRT
<213> Homo sapiens

<400> 26
Met Ala Pro Ala Ala Trp Leu Arg Ser Ala Ala Ala Arg Ala Leu Leu
 1               5                  10                  15
Pro Pro Met Leu Leu Leu Leu Leu Gln Pro Pro Pro Leu Leu Ala Arg
            20                  25                  30
Ala Leu Pro Pro Asp Val His His Leu His Ala Glu Arg Arg Gly Pro
        35                  40                  45
Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala
    50                  55                  60
Thr Gln Glu Ala Pro Arg Pro Ala Ser Ser Leu Arg Pro Pro Arg Cys
65                  70                  75                  80
Gly Val Pro Asp Pro Ser Asp Gly Leu Ser Ala Arg Asn Arg Gln Lys
                85                  90                  95
Arg Phe Val Leu Ser Gly Gly Arg Trp Glu Lys Thr Asp Leu Thr Tyr
            100                 105                 110
Arg Ile Leu Arg Phe Pro Trp Gln Leu Val Gln Glu Gln Val Arg Gln
        115                 120                 125
```

```
Thr Met Ala Glu Ala Leu Lys Val Trp Ser Asp Val Thr Pro Leu Thr
    130                 135                 140
Phe Thr Glu Val His Glu Gly Arg Ala Asp Ile Met Ile Asp Phe Ala
145                 150                 155                 160
Arg Tyr Trp Asp Gly Asp Asp Leu Pro Phe Asp Gly Pro Gly Gly Ile
                165                 170                 175
Leu Ala His Ala Phe Phe Pro Lys Thr His Arg Glu Gly Asp Val His
            180                 185                 190
Phe Asp Tyr Asp Glu Thr Trp Thr Ile Gly Asp Asp Gln Gly Thr Asp
        195                 200                 205
Leu Leu Gln Val Ala Ala His Glu Phe Gly His Val Leu Gly Leu Gln
    210                 215                 220
His Thr Thr Ala Ala Lys Ala Leu Met Ser Ala Phe Tyr Thr Phe Arg
225                 230                 235                 240
Tyr Pro Leu Ser Leu Ser Pro Asp Asp Cys Arg Gly Val Gln His Leu
                245                 250                 255
Tyr Gly Gln Pro Trp Pro Thr Val Thr Ser Arg Thr Pro Ala Leu Gly
            260                 265                 270
Pro Gln Ala Gly Ile Asp Thr Asn Glu Ile Ala Pro Leu Glu Pro Asp
        275                 280                 285
Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe Asp Ala Val Ser Thr Ile
    290                 295                 300
Arg Gly Glu Leu Phe Phe Phe Lys Ala Gly Phe Val Trp Arg Leu Arg
305                 310                 315                 320
Gly Gly Gln Leu Gln Pro Gly Tyr Pro Ala Leu Ala Ser Arg His Trp
                325                 330                 335
Gln Gly Leu Pro Ser Pro Val Asp Ala Ala Phe Glu Asp Ala Gln Gly
            340                 345                 350
His Ile Trp Phe Phe Gln Gly Ala Gln Tyr Trp Val Tyr Asp Gly Glu
        355                 360                 365
Lys Pro Val Leu Gly Pro Ala Pro Leu Thr Glu Leu Gly Leu Val Arg
    370                 375                 380
Phe Pro Val His Ala Ala Leu Val Trp Gly Pro Glu Lys Asn Lys Ile
385                 390                 395                 400
Tyr Phe Phe Arg Gly Arg Asp Tyr Trp Arg Phe His Pro Ser Thr Arg
                405                 410                 415
Arg Val Asp Ser Pro Val Pro Arg Arg Ala Thr Asp Trp Arg Gly Val
            420                 425                 430
Pro Ser Glu Ile Asp Ala Ala Phe Gln Asp Ala Asp Gly Tyr Ala Tyr
        435                 440                 445
Phe Leu Arg Gly Arg Leu Tyr Trp Lys Phe Asp Pro Val Lys Val Lys
    450                 455                 460
Ala Leu Glu Gly Phe Pro Arg Leu Val Gly Pro Asp Phe Phe Gly Cys
465                 470                 475                 480
Ala Glu Pro Ala Asn Thr Phe Leu
                485
```

<210> 27
<211> 582
<212> PRT
<213> Homo sapiens

<400> 27

```
Met Ser Pro Ala Pro Arg Pro Ser Arg Cys Leu Leu Leu Pro Leu Leu
 1               5                  10                  15
Thr Leu Gly Thr Ala Leu Ala Ser Leu Gly Ser Ala Gln Ser Ser Ser
            20                  25                  30
Phe Ser Pro Glu Ala Trp Leu Gln Gln Tyr Gly Tyr Leu Pro Pro Gly
```

```
Pro Arg Arg Pro Gly Arg Pro Asp His Arg Pro Pro Arg Pro Pro Gln
                325                 330                 335
Pro Pro Pro Pro Gly Gly Lys Pro Glu Arg Pro Pro Lys Pro Gly Pro
            340                 345                 350
Pro Val Gln Pro Arg Ala Thr Glu Arg Pro Asp Gln Tyr Gly Pro Asn
        355                 360                 365
Ile Cys Asp Gly Asp Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met
    370                 375                 380
Phe Val Phe Lys Gly Arg Trp Phe Trp Arg Val Arg His Asn Arg Val
385                 390                 395                 400
Leu Asp Asn Tyr Pro Met Pro Ile Gly His Phe Trp Arg Gly Leu Pro
                405                 410                 415
Gly Asp Ile Ser Ala Ala Tyr Glu Arg Gln Asp Gly Arg Phe Val Phe
            420                 425                 430
Phe Lys Gly Asp Arg Tyr Trp Leu Phe Arg Glu Ala Asn Leu Glu Pro
        435                 440                 445
Gly Tyr Pro Gln Pro Leu Thr Ser Tyr Gly Leu Gly Ile Pro Tyr Asp
    450                 455                 460
Arg Ile Asp Thr Ala Ile Trp Trp Glu Pro Thr Gly His Thr Phe Phe
465                 470                 475                 480
Phe Gln Glu Asp Arg Tyr Trp Arg Phe Asn Glu Glu Thr Gln Arg Gly
                485                 490                 495
Asp Pro Gly Tyr Pro Lys Pro Ile Ser Val Trp Gln Gly Ile Pro Ala
            500                 505                 510
Ser Pro Lys Gly Ala Phe Leu Ser Asn Asp Ala Ala Tyr Thr Tyr Phe
        515                 520                 525
Tyr Lys Gly Thr Lys Tyr Trp Lys Phe Asp Asn Glu Arg Leu Arg Met
    530                 535                 540
Glu Pro Gly Tyr Pro Lys Ser Ile Leu Arg Asp Phe Met Gly Cys Gln
545                 550                 555                 560
Glu His Val Glu Pro Gly Pro Arg Trp Pro Asp Val Ala Arg Pro Pro
                565                 570                 575
Phe Asn Pro His Gly Gly Ala Glu Pro Gly Ala Asp Ser Ala Glu Gly
            580                 585                 590
Asp Val Gly Asp Gly Asp Gly Asp Phe Gly Ala Gly Val Asn Lys Asp
        595                 600                 605
Gly Gly Ser Arg Val Val Val Gln Met Glu Glu Val Ala Arg Thr Val
    610                 615                 620
Asn Val Val Met Val Leu Val Pro Leu Leu Leu Leu Leu Cys Val Leu
625                 630                 635                 640
Gly Leu Thr Tyr Ala Leu Val Gln Met Gln Arg Lys Gly Ala Pro Arg
                645                 650                 655
Val Leu Leu Tyr Cys Lys Arg Ser Leu Gln Glu Trp Val
            660                 665
```

<210> 29
<211> 607
<212> PRT
<213> Homo sapiens

<400> 29

```
Met Ile Leu Leu Thr Phe Ser Thr Gly Arg Arg Leu Asp Phe Val His
 1               5                  10                  15
His Ser Gly Val Phe Phe Leu Gln Thr Leu Leu Trp Ile Leu Cys Ala
            20                  25                  30
Thr Val Cys Gly Thr Glu Gln Tyr Phe Asn Val Glu Val Trp Leu Gln
        35                  40                  45
Lys Tyr Gly Tyr Leu Pro Pro Thr Asp Pro Arg Met Ser Val Leu Arg
```

```
     50                  55                  60
Ser Ala Glu Thr Met Gln Ser Ala Leu Ala Ala Met Gln Gln Phe Tyr
65                  70                  75                  80
Gly Ile Asn Met Thr Gly Lys Val Asp Arg Asn Thr Ile Asp Trp Met
                85                  90                  95
Lys Lys Pro Arg Cys Gly Val Pro Asp Gln Thr Arg Gly Ser Ser Lys
            100                 105                 110
Phe His Ile Arg Arg Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Gln
        115                 120                 125
His Lys His Ile Thr Tyr Ser Ile Lys Asn Val Thr Pro Lys Val Gly
    130                 135                 140
Asp Pro Glu Thr Arg Lys Ala Ile Arg Arg Ala Phe Asp Val Trp Gln
145                 150                 155                 160
Asn Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr Ser Glu Leu Glu
                165                 170                 175
Asn Gly Lys Arg Asp Val Asp Ile Thr Ile Ile Phe Ala Ser Gly Phe
            180                 185                 190
His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His
        195                 200                 205
Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser
    210                 215                 220
Asp Glu Pro Trp Thr Leu Gly Asn Pro Asn His Asp Gly Asn Asp Leu
225                 230                 235                 240
Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His
                245                 250                 255
Ser Asn Asp Pro Thr Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu
            260                 265                 270
Thr Asp Asn Phe Lys Leu Pro Asn Asp Asp Leu Gln Gly Ile Gln Lys
        275                 280                 285
Ile Tyr Gly Pro Pro Asp Lys Ile Pro Pro Pro Thr Arg Pro Leu Pro
    290                 295                 300
Thr Val Pro Pro His Arg Ser Ile Pro Pro Ala Asp Pro Arg Lys Asn
305                 310                 315                 320
Asp Arg Pro Lys Pro Pro Arg Pro Pro Thr Gly Arg Pro Ser Tyr Pro
                325                 330                 335
Gly Ala Lys Pro Asn Ile Cys Asp Gly Asn Phe Asn Thr Leu Ala Ile
            340                 345                 350
Leu Arg Arg Glu Met Phe Val Phe Lys Asp Gln Trp Phe Trp Arg Val
        355                 360                 365
Arg Asn Asn Arg Val Met Asp Gly Tyr Pro Met Gln Ile Thr Tyr Phe
    370                 375                 380
Trp Arg Gly Leu Pro Pro Ser Ile Asp Ala Val Tyr Glu Asn Ser Asp
385                 390                 395                 400
Gly Asn Phe Val Phe Phe Lys Gly Asn Lys Tyr Trp Val Phe Lys Asp
                405                 410                 415
Thr Thr Leu Gln Pro Gly Tyr Pro His Asp Leu Ile Thr Leu Gly Ser
            420                 425                 430
Gly Ile Pro Pro His Gly Ile Asp Ser Ala Ile Trp Trp Glu Asp Val
        435                 440                 445
Gly Lys Thr Tyr Phe Phe Lys Gly Asp Arg Tyr Trp Arg Tyr Ser Glu
    450                 455                 460
Glu Met Lys Thr Met Asp Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp
465                 470                 475                 480
Lys Gly Ile Pro Glu Ser Pro Gln Gly Ala Phe Val His Lys Glu Asn
                485                 490                 495
Gly Phe Thr Tyr Phe Tyr Lys Gly Lys Glu Tyr Trp Lys Phe Asn Asn
            500                 505                 510
Gln Ile Leu Lys Val Glu Pro Gly Tyr Pro Arg Ser Ile Leu Lys Asp
```

```
        515                 520                 525
Phe Met Gly Cys Asp Gly Pro Thr Asp Arg Val Lys Glu Gly His Ser
    530                 535                 540
Pro Pro Asp Asp Val Asp Ile Val Ile Lys Leu Asp Asn Thr Ala Ser
545                 550                 555                 560
Thr Val Lys Ala Ile Ala Ile Val Ile Pro Cys Ile Leu Ala Leu Cys
                565                 570                 575
Leu Leu Val Leu Val Tyr Thr Val Phe Gln Phe Lys Arg Lys Gly Thr
            580                 585                 590
Pro Arg His Ile Leu Tyr Cys Lys Arg Ser Met Gln Glu Trp Val
        595                 600                 605

<210> 30
<211> 519
<212> PRT
<213> Homo sapiens

<400> 30
Met Gln Gln Phe Gly Gly Leu Glu Ala Thr Gly Ile Leu Asp Glu Ala
 1               5                  10                  15
Thr Leu Ala Leu Met Lys Thr Pro Arg Cys Ser Leu Pro Asp Leu Pro
            20                  25                  30
Val Leu Thr Gln Ala Arg Arg Arg Arg Gln Ala Pro Ala Pro Thr Lys
        35                  40                  45
Trp Asn Lys Arg Asn Leu Ser Trp Arg Val Arg Thr Phe Pro Arg Asp
    50                  55                  60
Ser Pro Leu Gly His Asp Thr Val Arg Ala Leu Met Tyr Tyr Ala Leu
65                  70                  75                  80
Lys Val Trp Ser Asp Ile Ala Pro Leu Asn Phe His Glu Val Ala Gly
                85                  90                  95
Ser Thr Ala Asp Ile Gln Ile Asp Phe Ser Lys Ala Asp His Asn Asp
            100                 105                 110
Gly Tyr Pro Phe Asp Gly Pro Gly Gly Thr Val Ala His Ala Phe Phe
        115                 120                 125
Pro Gly His His His Thr Ala Gly Asp Thr His Phe Asp Asp Asp Glu
    130                 135                 140
Ala Trp Thr Phe Arg Ser Ser Asp Ala His Gly Met Asp Leu Phe Ala
145                 150                 155                 160
Val Ala Val His Glu Phe Gly His Ala Ile Gly Leu Ser His Val Ala
                165                 170                 175
Ala Ala His Ser Ile Met Arg Pro Tyr Tyr Gln Gly Pro Val Gly Asp
            180                 185                 190
Pro Leu Arg Tyr Gly Leu Pro Tyr Glu Asp Lys Val Arg Val Trp Gln
        195                 200                 205
Leu Tyr Gly Val Arg Glu Ser Val Ser Pro Thr Ala Gln Pro Glu Glu
    210                 215                 220
Pro Pro Leu Leu Pro Glu Pro Pro Asp Asn Arg Ser Ser Ala Pro Pro
225                 230                 235                 240
Arg Lys Asp Val Pro His Arg Cys Ser Thr His Phe Asp Ala Val Ala
                245                 250                 255
Gln Ile Arg Gly Glu Ala Phe Phe Phe Lys Gly Lys Tyr Phe Trp Arg
            260                 265                 270
Leu Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln Met His
        275                 280                 285
Arg Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp Ala Val
    290                 295                 300
Tyr Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly Asp Arg
305                 310                 315                 320
```

```
Tyr Trp Val Phe Lys Asp Asn Asn Val Glu Glu Gly Tyr Pro Arg Pro
                325                 330                 335
Val Ser Asp Phe Ser Leu Pro Pro Gly Gly Ile Asp Ala Ala Phe Ser
            340                 345                 350
Trp Ala His Asn Asp Arg Thr Tyr Phe Phe Lys Asp Gln Leu Tyr Trp
        355                 360                 365
Arg Tyr Asp Asp His Thr Arg His Met Asp Pro Gly Tyr Pro Ala Gln
    370                 375                 380
Ser Pro Leu Trp Arg Gly Val Pro Ser Thr Leu Asp Asp Ala Met Arg
385                 390                 395                 400
Trp Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr Trp Lys
                405                 410                 415
Val Leu Asp Gly Glu Leu Glu Val Ala Pro Gly Tyr Pro Gln Ser Thr
            420                 425                 430
Ala Arg Asp Trp Leu Val Cys Gly Asp Ser Gln Ala Asp Gly Ser Val
        435                 440                 445
Ala Ala Gly Val Asp Ala Ala Glu Gly Pro Arg Ala Pro Pro Gly Gln
    450                 455                 460
His Asp Gln Ser Arg Ser Glu Asp Gly Tyr Glu Val Cys Ser Cys Thr
465                 470                 475                 480
Ser Gly Ala Ser Ser Pro Pro Gly Ala Pro Gly Pro Leu Val Ala Ala
                485                 490                 495
Thr Met Leu Leu Leu Leu Pro Pro Leu Ser Pro Gly Ala Leu Trp Thr
            500                 505                 510
Ala Ala Gln Ala Leu Thr Leu
        515
```

<210> 31
<211> 508
<212> PRT
<213> Homo sapiens

<400> 31

```
Met Asn Cys Gln Gln Leu Trp Leu Gly Phe Leu Leu Pro Met Thr Val
 1               5                  10                  15
Ser Gly Arg Val Leu Gly Leu Ala Glu Val Ala Pro Val Asp Tyr Leu
            20                  25                  30
Ser Gln Tyr Gly Tyr Leu Gln Lys Pro Leu Glu Gly Ser Asn Asn Phe
        35                  40                  45
Lys Pro Glu Asp Ile Thr Glu Ala Leu Arg Ala Phe Gln Glu Ala Ser
    50                  55                  60
Glu Leu Pro Val Ser Gly Gln Leu Asp Asp Ala Thr Arg Ala Arg Met
65                  70                  75                  80
Arg Gln Pro Arg Cys Gly Leu Glu Asp Pro Phe Asn Gln Lys Thr Leu
                85                  90                  95
Lys Tyr Leu Leu Leu Gly Arg Trp Arg Lys Lys His Leu Thr Phe Arg
            100                 105                 110
Ile Leu Asn Leu Pro Ser Thr Leu Pro Pro His Thr Ala Arg Ala Ala
        115                 120                 125
Leu Arg Gln Ala Phe Gln Asp Trp Ser Asn Val Ala Pro Leu Thr Phe
    130                 135                 140
Gln Glu Val Gln Ala Gly Ala Ala Asp Ile Arg Leu Ser Phe His Gly
145                 150                 155                 160
Arg Gln Ser Ser Tyr Cys Ser Asn Thr Phe Asp Gly Pro Gly Arg Val
                165                 170                 175
Leu Ala His Ala Asp Ile Pro Glu Leu Gly Ser Val His Phe Asp Glu
            180                 185                 190
Asp Glu Phe Trp Thr Glu Gly Thr Tyr Arg Gly Val Asn Leu Arg Ile
```

```
        195                 200                 205
Ile Ala Ala His Glu Val Gly His Ala Leu Gly Leu Gly His Ser Arg
    210                 215                 220
Tyr Ser Gln Ala Leu Met Ala Pro Val Tyr Glu Gly Tyr Arg Pro His
225                 230                 235                 240
Phe Lys Leu His Pro Asp Asp Val Ala Gly Ile Gln Ala Leu Tyr Gly
                245                 250                 255
Lys Lys Ser Pro Val Ile Arg Asp Glu Glu Glu Glu Glu Thr Glu Leu
            260                 265                 270
Pro Thr Val Pro Pro Val Pro Thr Glu Pro Ser Pro Met Pro Asp Pro
        275                 280                 285
Cys Ser Ser Glu Leu Asp Ala Met Met Leu Gly Pro Arg Gly Lys Thr
    290                 295                 300
Tyr Ala Phe Lys Gly Asp Tyr Val Trp Thr Val Ser Asp Ser Gly Pro
305                 310                 315                 320
Gly Pro Leu Phe Arg Val Ser Ala Leu Trp Glu Gly Leu Pro Gly Asn
                325                 330                 335
Leu Asp Ala Ala Val Tyr Ser Pro Arg Thr Gln Trp Ile His Phe Phe
            340                 345                 350
Lys Gly Asp Lys Val Trp Arg Tyr Ile Asn Phe Lys Met Ser Pro Gly
        355                 360                 365
Phe Pro Lys Lys Leu Asn Arg Val Glu Pro Asn Leu Asp Ala Ala Leu
    370                 375                 380
Tyr Trp Pro Leu Asn Gln Lys Val Phe Leu Phe Lys Gly Ser Gly Tyr
385                 390                 395                 400
Trp Gln Trp Asp Glu Leu Ala Arg Thr Asp Phe Ser Ser Tyr Pro Lys
                405                 410                 415
Pro Ile Lys Gly Leu Phe Thr Gly Val Pro Asn Gln Pro Ser Ala Ala
            420                 425                 430
Met Ser Trp Gln Asp Gly Arg Val Tyr Phe Phe Lys Gly Lys Val Tyr
        435                 440                 445
Trp Arg Leu Asn Gln Gln Leu Arg Val Glu Lys Gly Tyr Pro Arg Asn
    450                 455                 460
Ile Ser His Asn Trp Met His Cys Arg Pro Arg Thr Ile Asp Thr Thr
465                 470                 475                 480
Pro Ser Gly Gly Asn Thr Thr Pro Ser Gly Thr Gly Ile Thr Leu Asp
                485                 490                 495
Thr Thr Leu Ser Ala Thr Glu Thr Thr Phe Glu Tyr
            500                 505
```

<210> 32
<211> 471
<212> PRT
<213> Homo sapiens

<400> 32

```
Met His Pro Gly Val Leu Ala Ala Phe Leu Phe Leu Ser Trp Thr His
 1               5                  10                  15
Cys Arg Ala Leu Pro Leu Pro Ser Gly Gly Asp Glu Asp Asp Leu Ser
            20                  25                  30
Glu Glu Asp Leu Gln Phe Ala Glu Arg Tyr Leu Arg Ser Tyr Tyr His
        35                  40                  45
Pro Thr Asn Leu Ala Gly Ile Leu Lys Glu Asn Ala Ala Ser Ser Met
    50                  55                  60
Thr Glu Arg Leu Arg Glu Met Gln Ser Phe Phe Gly Leu Glu Val Thr
65                  70                  75                  80
Gly Lys Leu Asp Asp Asn Thr Leu Asp Val Met Lys Lys Pro Arg Cys
                85                  90                  95
```

```
Gly Val Pro Asp Val Gly Glu Tyr Asn Val Phe Pro Arg Thr Leu Lys
            100                 105                 110
Trp Ser Lys Met Asn Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp
        115                 120                 125
Met Thr His Ser Glu Val Glu Lys Ala Phe Lys Lys Ala Phe Lys Val
    130                 135                 140
Trp Ser Asp Val Thr Pro Leu Asn Phe Thr Arg Leu His Asp Gly Ile
145                 150                 155                 160
Ala Asp Ile Met Ile Ser Phe Gly Ile Lys Glu His Gly Asp Phe Tyr
                165                 170                 175
Pro Phe Asp Gly Pro Ser Gly Leu Leu Ala His Ala Phe Pro Pro Gly
            180                 185                 190
Pro Asn Tyr Gly Gly Asp Ala His Phe Asp Asp Asp Glu Thr Trp Thr
        195                 200                 205
Ser Ser Ser Lys Gly Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe
    210                 215                 220
Gly His Ser Leu Gly Leu Asp His Ser Lys Asp Pro Gly Ala Leu Met
225                 230                 235                 240
Phe Pro Ile Tyr Thr Tyr Thr Gly Lys Ser His Phe Met Leu Pro Asp
                245                 250                 255
Asp Asp Val Gln Gly Ile Gln Ser Leu Tyr Gly Pro Gly Asp Glu Asp
            260                 265                 270
Pro Asn Pro Lys His Pro Lys Thr Pro Asp Lys Cys Asp Pro Ser Leu
        275                 280                 285
Ser Leu Asp Ala Ile Thr Ser Leu Arg Gly Glu Thr Met Ile Phe Lys
    290                 295                 300
Asp Arg Phe Phe Trp Arg Leu His Pro Gln Gln Val Asp Ala Glu Leu
305                 310                 315                 320
Phe Leu Thr Lys Ser Phe Trp Pro Glu Leu Pro Asn Arg Ile Asp Ala
                325                 330                 335
Ala Tyr Glu His Pro Ser His Asp Leu Ile Phe Ile Phe Arg Gly Arg
            340                 345                 350
Lys Phe Trp Ala Leu Asn Gly Tyr Asp Ile Leu Glu Gly Tyr Pro Lys
        355                 360                 365
Lys Ile Ser Glu Leu Gly Leu Pro Lys Glu Val Lys Lys Ile Ser Ala
    370                 375                 380
Ala Val His Phe Glu Asp Thr Gly Lys Thr Leu Leu Phe Ser Gly Asn
385                 390                 395                 400
Gln Val Trp Arg Tyr Asp Asp Thr Asn His Ile Met Asp Lys Asp Tyr
                405                 410                 415
Pro Arg Leu Ile Glu Glu Asp Phe Pro Gly Ile Gly Asp Lys Val Asp
            420                 425                 430
Ala Val Tyr Glu Lys Asn Gly Tyr Ile Tyr Phe Phe Asn Gly Pro Ile
        435                 440                 445
Gln Phe Glu Tyr Ser Ile Trp Ser Asn Arg Ile Val Arg Val Met Pro
    450                 455                 460
Ala Asn Ser Ile Leu Trp Cys
465                 470

<210> 33
<211> 183
<212> PRT
<213> Homo sapiens

<400> 33
Met Asp Pro Gly Thr Val Ala Thr Met Arg Lys Pro Arg Cys Ser Leu
 1               5                  10                  15
Pro Asp Val Leu Gly Val Ala Gly Leu Val Arg Arg Arg Arg Arg Tyr
```

```
            20                  25                  30
Ala Leu Ser Gly Ser Val Trp Lys Lys Arg Thr Leu Thr Trp Arg Val
        35                  40                  45
Arg Ser Phe Pro Gln Ser Ser Gln Leu Ser Gln Glu Thr Val Arg Val
    50                  55                  60
Leu Met Ser Tyr Ala Leu Met Ala Trp Gly Met Glu Ser Gly Leu Thr
65                  70                  75                  80
Phe His Glu Val Asp Ser Pro Gln Gly Gln Glu Pro Asp Ile Leu Ile
                85                  90                  95
Asp Phe Ala Arg Ala Phe His Gln Asp Ser Tyr Pro Phe Asp Gly Leu
            100                 105                 110
Gly Gly Thr Leu Ala His Ala Phe Phe Pro Gly Glu His Pro Ile Ser
        115                 120                 125
Gly Asp Thr His Phe Asp Asp Glu Glu Thr Trp Thr Phe Gly Ser Lys
    130                 135                 140
Ala Ser Gln Gln Leu Glu Gln Glu Leu Ala Gly Gly Ser Pro Val Asp
145                 150                 155                 160
Glu Glu Leu Gly Phe Ser Arg Gly Trp Arg Val Asn Pro Leu Gly Pro
                165                 170                 175
Gly Ser Pro Glu Arg Leu Ser
            180

<210> 34
<211> 390
<212> PRT
<213> Homo sapiens

<400> 34
Met Gly Arg Gly Ala Arg Val Pro Ser Glu Ala Pro Gly Ala Gly Val
 1               5                  10                  15
Glu Arg Arg Trp Leu Gly Ala Ala Leu Val Ala Leu Cys Leu Leu Pro
            20                  25                  30
Ala Leu Val Leu Leu Ala Arg Leu Gly Ala Pro Ala Val Pro Ala Trp
        35                  40                  45
Ser Ala Ala Gln Gly Asp Val Ala Ala Leu Gly Leu Ser Ala Val Pro
    50                  55                  60
Pro Thr Arg Val Pro Gly Pro Leu Ala Pro Arg Arg Arg Arg Tyr Thr
65                  70                  75                  80
Leu Thr Pro Ala Arg Leu Arg Trp Asp His Phe Asn Leu Thr Tyr Arg
                85                  90                  95
Ile Leu Ser Phe Pro Arg Asn Leu Leu Ser Pro Arg Glu Thr Arg Arg
            100                 105                 110
Ala Leu Ala Ala Ala Phe Arg Met Trp Ser Asp Val Ser Pro Phe Ser
        115                 120                 125
Phe Arg Glu Val Ala Pro Glu Gln Pro Ser Asp Leu Arg Ile Gly Phe
    130                 135                 140
Tyr Pro Ile Asn His Thr Asp Cys Leu Val Ser Ala Leu His His Cys
145                 150                 155                 160
Phe Asp Gly Pro Thr Gly Glu Leu Ala His Ala Phe Phe Pro Pro His
                165                 170                 175
Gly Gly Ile His Phe Asp Asp Ser Glu Tyr Trp Val Leu Gly Pro Thr
            180                 185                 190
Arg Tyr Ser Trp Lys Lys Gly Val Trp Leu Thr Asp Leu Val His Val
        195                 200                 205
Ala Ala His Glu Ile Gly His Ala Leu Gly Leu Met His Ser Gln His
    210                 215                 220
Gly Arg Ala Leu Met His Leu Asn Ala Thr Leu Arg Gly Trp Lys Ala
225                 230                 235                 240
```

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Leu Ser Gln Asp Glu Leu Trp Gly Leu His Arg Leu Tyr Gly Cys Leu
                245                 250                 255
Asp Arg Leu Phe Val Cys Ala Ser Trp Ala Arg Arg Gly Phe Cys Asp
            260                 265                 270
Ala Arg Arg Arg Leu Met Lys Arg Leu Cys Pro Ser Ser Cys Asp Phe
        275                 280                 285
Cys Tyr Glu Phe Pro Phe Pro Thr Val Ala Thr Thr Pro Pro Pro Pro
    290                 295                 300
Arg Thr Lys Thr Arg Leu Val Pro Glu Gly Arg Asn Val Thr Phe Arg
305                 310                 315                 320
Cys Gly Gln Lys Ile Leu His Lys Lys Gly Lys Val Tyr Trp Tyr Lys
                325                 330                 335
Asp Gln Glu Pro Leu Glu Phe Ser Tyr Pro Gly Tyr Leu Ala Leu Gly
            340                 345                 350
Glu Ala His Leu Ser Ile Ile Ala Asn Ala Val Asn Glu Gly Thr Tyr
        355                 360                 365
Thr Cys Val Val Arg Arg Gln Gln Arg Val Leu Thr Thr Tyr Ser Trp
    370                 375                 380
Arg Val Arg Val Arg Gly
385                 390

<210> 35
<211> 660
<212> PRT
<213> Homo sapiens

<400> 35
Met Glu Ala Leu Met Ala Arg Gly Ala Leu Thr Gly Pro Leu Arg Ala
 1               5                  10                  15
Leu Cys Leu Leu Gly Cys Leu Leu Ser His Ala Ala Ala Ala Pro Ser
            20                  25                  30
Pro Ile Ile Lys Phe Pro Gly Asp Val Ala Pro Lys Thr Asp Lys Glu
        35                  40                  45
Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser
    50                  55                  60
Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe
65                  70                  75                  80
Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr
                85                  90                  95
Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe
            100                 105                 110
Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile
        115                 120                 125
Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe
    130                 135                 140
Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser
145                 150                 155                 160
Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp
                165                 170                 175
Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala
            180                 185                 190
His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp
        195                 200                 205
Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys
    210                 215                 220
Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn
225                 230                 235                 240
Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe
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                245                 250                 255
Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly
            260                 265                 270
Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly
        275                 280                 285
Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser
    290                 295                 300
Cys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys Gly Thr Thr
305                 310                 315                 320
Glu Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro Glu Thr Ala
                325                 330                 335
Met Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys Val Phe Pro
            340                 345                 350
Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg
        355                 360                 365
Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp
    370                 375                 380
Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val
385                 390                 395                 400
Ala Ala His Glu Phe Gly His Ala Met Gly Leu Glu His Ser Gln Asp
                405                 410                 415
Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg
            420                 425                 430
Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser
        435                 440                 445
Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val
    450                 455                 460
Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln
465                 470                 475                 480
Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr
                485                 490                 495
Val Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val Ala Thr Phe
            500                 505                 510
Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
        515                 520                 525
Glu Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp Ile Tyr Ser
    530                 535                 540
Ala Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr Ser Leu Gly
545                 550                 555                 560
Leu Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn Trp Ser Lys
                565                 570                 575
Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn
            580                 585                 590
Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
        595                 600                 605
Ala Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val Asp Leu Gln
    610                 615                 620
Gly Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr Leu Lys Leu
625                 630                 635                 640
Glu Asn Gln Ser Leu Lys Ser Val Lys Phe Gly Ser Ile Lys Ser Asp
                645                 650                 655
Trp Leu Gly Cys
            660
```

<210> 36
<211> 707
<212> PRT
<213> Homo sapiens

<400> 36
Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
1 5 10 15
Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
20 25 30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
35 40 45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
50 55 60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
65 70 75 80
Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
85 90 95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
100 105 110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
115 120 125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
130 135 140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
145 150 155 160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
165 170 175
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
180 185 190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
195 200 205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
210 215 220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
225 230 235 240
Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
245 250 255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
260 265 270
Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
275 280 285
Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
290 295 300
Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
305 310 315 320
Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
325 330 335
Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
340 345 350
Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
355 360 365
Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
370 375 380
Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
385 390 395 400
His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
405 410 415
Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
420 425 430
Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
435 440 445

```
Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
    450                 455                 460
Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
465                 470                 475                 480
Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
                485                 490                 495
Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
            500                 505                 510
Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
        515                 520                 525
Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
    530                 535                 540
Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
545                 550                 555                 560
Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
                565                 570                 575
Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
            580                 585                 590
Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
        595                 600                 605
Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
    610                 615                 620
Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
625                 630                 635                 640
Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
                645                 650                 655
Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
            660                 665                 670
Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
        675                 680                 685
Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
    690                 695                 700
Pro Glu Asp
705
```

<210> 37
<211> 16
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (3)...(5)
<223> Xaa = any amino acid

<221> VARIANT
<222> (7)...(7)
<223> Xaa = any amino acid

<221> VARIANT
<222> (11)...(12)
<223> Xaa = any amino acid

<221> VARIANT
<222> (13)...(13)
<223> Xaa = Glycine or Alanine

<400> 37

His Gly Xaa Xaa Xaa Pro Xaa Phe Asp Gly Xaa Xaa Xaa His Ala Phe
1 5 10 15